Symposium 205

New Treatment Targets in Gut and Liver Diseases

October 21 – 22, 2016
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Symposium 205

NEW TREATMENT TARGETS
IN GUT AND LIVER DISEASES

Lucerne, Switzerland
October 21 – 22, 2016

Scientific Organization:
M. Allez, Paris (France)
C. Fiocchi, Cleveland (USA)
H. Herfarth, Chapel Hill (USA)
B. Müllhaupt, Zurich (Switzerland)
G. Rogler, Zurich (Switzerland)
S. Vavricka, Zurich (Switzerland)
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101. Potential non-invasive biomarkers of liver fibrosis in chronic hepatitis B infection
A. Woziwodzka, M. Rybicka, A. Sznarkowska, T. Romanowski, P. Stalke, M. Dreczewski, K.P. Bielawski (Gdansk, PL)

102. The results of combined treatment of Helicobacter pylori associated stomach MALT lymphoma
A.A. Yusupbekov, J. Ismailova, M.M. Mallaev (Tashkent, UZ)

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Session I

Viral hepatitis
The role of the innate and adaptive immune response in chronic viral hepatitis

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Innate and adaptive immune responses closely interact in order to limit, contain, and eliminate hepatitis viruses after acute infection of the host. In a majority of patients infected with hepatitis C virus (HCV), in varying frequencies of patients infected with hepatitis B (HBV) with or without hepatitis D virus (HDV) co-infection, and in some immunocompromised patients infected with hepatitis E virus (HDV), however, the host’s immune response fails and chronic infection evolves. Several mechanisms contribute to this failure of the host’s antiviral immune response: Evasion from innate immunity includes e.g. viral stealth and hiding from innate immunity (HBV) as well as cleavage of innate signaling molecules by viral proteases (HCV). Evasion from neutralizing antibodies includes mutational viral escape as well as cell-to-cell transmission. Main mechanisms of virus-specific T cell failure are viral escape from virus-specific CD8+ T cells (most commonly described for HCV, but with growing evidence also for HBV and HDV), as well as exhaustion of virus-specific CD8+ T cells due to diverse underlying pathways.

Understanding the mechanisms of successful antiviral immunity is not only intriguing from a scientific point of view, but may also have important clinical implications. This is most evident in chronic HBV mono- and HBV/HDV co-infection. Chronic HBV infection can only rarely be cured, requiring long-term, if not life-long, antiviral therapy in many patients. Therapeutic vaccination and/or immunomodulation, e.g. targeting inhibitory T cell receptors or boosting innate immunity, may allow for HBV elimination in a larger number of patients. In chronic HBV/HDV co-infection, for the vast majority of patients no effective treatment is available until now, underlining the urgent need for new therapeutic concepts such as immunotherapy. In chronic HCV infection, despite coming at high cost for the health care system, direct-acting antivirals allow viral eradication without relevant side effect in nearly all patients. Global eradication, however, will also require the successful development of prophylactic vaccination. Indeed, promising vaccination trials are currently ongoing in cohorts at high risk for HCV infection.
Hepatitis B: Current challenges in diagnosis and treatment

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Diagnosis of HBV infection and of HBV-related liver disease is traditionally based upon the assessment of virological, serological markers as well as liver function tests, imaging techniques, non-invasive tests for fibrosis and liver biopsy. Five different phases of the HBV infection can be recognized, each one characterized by specific clinical and virological features which define the priority for antiviral treatment or follow-up. There are no specific challenges to the diagnosis of HBV in countries where all these diagnostic tests are available and fully reimbursed.

Antiviral therapy of chronic hepatitis B virus (HBV) infection is aimed to stop viral replication in order to improve patient survival by preventing progression to cirrhosis, end-stage liver disease or hepatocellular carcinoma (HCC). The first-line drugs recommended in naïve patients are pegylated-interferon (Peg-IFN) and such a third generation nucleot(s)ide analogues (NUC) as entecavir (ETV) or tenofovir (TDF). Short-term treatment with Peg-IFN results in a sustained immune control of the infection in nearly 30% of the patients leading to hepatitis B surface antigen (HBsAg) seroclearance in approximately one third of responders. However, the widespread adoption of this strategy is hampered by tolerability issues and limited effectiveness. It is currently indicated in young to middle aged patients with mild to moderate liver disease and good baseline predictors of response. For all the other patients, NUC therapy is the preferred choice. Long-term administration of ETV or TDF rapidly suppresses viral replication and normalizes ALT levels in most patients, reducing liver inflammation and fibrosis, preventing the progression to cirrhosis and clinical decompensation. HCC remains the only cause of morbidity and mortality in NUC treated patients, calling for a strict surveillance program in these patients despite fully suppression of viral replication. HBsAg seroconversion, the best and safest stopping rule for NUC, is unfortunately a rare event, this translating into the need of long-term, possibly lifelong, administration of oral therapies. Challenges to NUC therapy include the management of young patients with mild liver disease and high viremia, the safety of TDF in selected settings, the low HBeAg/HBsAg seroconversion rates, the residual risk of HCC risk and the cost, compliance, resistance, safety for treatments extended beyond 8 years. Combination of NUC and Peg-IFN either as a “de novo”, “add-on” or as a “switch to” strategy has been attempted on the assumption that the direct antiviral action of NUC may improve the immunomodulatory action of Peg-IFN leading to higher rates of responses, and vice versa. However, this approaches is not currently recommended in clinical practice because of unproven long-term superior efficacy. New anti-HBV strategies aimed to improve HBsAg kinetics in patients on long-term effective NUC treatment or to shorten the duration of therapy for NUC naïve patients are being assessed by clinical trials.
References:

Hepatitis C – What are the remaining problems?

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The hepatitis C virus chronically infects 60–180 million individuals worldwide and still represents a significant health care burden. The clinical course depends on a number of modifiable (alcohol, co-infections with hepatitis B virus or HIV and non-alcoholic fatty liver disease) and unmodifiable factors (age at the time of infection, sex, genotype 3, and host genetics). The infection can ultimately lead to liver cirrhosis and hepatocellular cancer (HCC) and HCV cirrhosis with or without HCC is still one of the most frequent indication for liver transplantation in the Western world.

Over the last years a significant number of direct acting antivirals (DAA) have been approved. Compared to the previous standard treatment, pegylated interferon and ribavirin, these new interferon-free combinations have simplified and shortened HCV treatment significantly, while at the same time increasing the sustained virological response rate (SVR) to 90% or higher for almost all patients groups. Patient populations previously considered as difficult to treat such as e.g. patients with decompensated liver cirrhosis. transplant recipients, patients on methadone substitution or difficult to cure such as e.g. patients with genotype 1 infection, patients with cirrhosis, HCV-HIV co-infected patients are no longer considered as difficult to treat and cure.

However, some patient groups still remain a challenge for the clinicians, such as patients with decompensated cirrhosis, patients with genotype 3 infection, patients on hemodialysis and patients, who fail DAA treatment.

In contrast to the interferon area, where patients with decompensated cirrhosis could not be treated, the current, well tolerated DAA regimens allows to treat even these patient groups. SVR is associated with improvement in liver function and might obviate the need for liver transplantation. However, with increasing disease severity (Child Pugh C compared to Child Pugh A/B) SVR is decreasing. In addition, the best strategy for treating patients with decompensated cirrhosis on the waiting list still needs to be defined.

Patients with genotype 3 infection used to be considered as easy to treat. In the DAA era this patient group proved to be a new difficult to treat patient group, especially treatment experienced patients with cirrhosis. The recent approval of the fixed dose combination sofosbuvir and velpatasvir as well as the imminent approval of ABT-493 (glecaprevir) und ABT-530 (pibrentasvir) might improve the outlook for this patient group as well.

Sofosbuvir, the backbone of many DAA combinations, is not approved for use in patients with a creatinine clearance below 30 ml/min. Therefore treatment options for patients with kidney failure are limited. The 3D combination with paritaprevir boosted with ritonavir, ombitasvir and dasabuvir with or without ribavirin is not renally cleared
and therefore a valuable option at least for genotype 1 patients. The recent approval of elbasvir and grazoprevir further improved the treatment options for this patients group on dialysis.

Treatment failures after DAA treatment, even in real life situations, are rare. However, those experiencing a virological relapse very often harbor a viral population with resistance associated substitutions (RAS). This might be “the real difficult to cure” population of the future.

Finally, the most difficult challenge of the future might be to identify the so far undiagnosed patients with chronic HCV infections and to provide access to treatment for all patients irrespective of fibrosis stage.
Hepatitis E: More than just a liver disease?

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As HEV has emerged as a hepatotropic virus of importance worldwide, our understanding of the effects of HEV on organs other than the liver is becoming clearer. HEV-associated extrahepatic manifestations occur in developed (HEV3) and developing (HEV1) countries and in acute and chronic (HEV3 only) infection. The range of organ systems affected is broad and includes neurological, renal, haematological and other miscellaneous pathologies. The best documented extrahepatic effects of HEV are neurological, with nearly 100 cases described worldwide, including Guillain-Barré syndrome, neuralgic amyotrophy and encephalitis/myelitis. Clinical and \textit{in vitro} and \textit{in vivo} laboratory data support a causal relationship between HEV and these neurological syndromes. HEV is also associated with a range of renal pathology, including membranoproliferative glomerulonephritis, membranous glomerulonephritis and IgA nephropathy. Clinical data suggest that this relationship is also likely to be causal. Causality remains to be established in the other extrahepatic manifestations of HEV. Many questions remain regarding the effects of HEV in organs other than the liver. These are of clinical importance to a range of physicians who are not Hepatologists. A full understanding of the extrahepatic manifestations of HEV is also crucial to Public Health specialists and policy makers when attempting to calculate the burden of this still emerging global infection.
Session II

Cholestatic liver disease
Molecular pathogenesis of cholestatic liver diseases

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Bile formation requires the interplay of a complex system of transport proteins in the plasma membrane of hepatocytes. Cholestasis is an impairment of bile formation and leads to accumulation of bile salts in hepatocytes and if persistent to cell injury and cholestatic liver disease. Cloning of the transport proteins relevant for bile formation allowed establishing the role of transporters in the molecular pathogenesis of cholestasis. Inherited forms of cholestasis due to mutations in transporters are very rare. In contrast, acquired forms of cholestasis are more frequent and mechanisms leading to such cholestatic liver diseases may be complex, but often involve the inhibition of transporters by endogenous substances or by drugs and/or their metabolites. In vitro experiments with BSEP are a well-established tool to retrospectively explain e.g. forms of drug-induced cholestasis. In contrast, in vitro experiments with MDR3 for testing the inhibitory potential of substances on biliary lipid secretion are challenging, but new assay systems allow demonstrating the inhibition of MDR3 by drugs. Shot gun determination of the proteome of the rat canalicular membrane revealed the expression of several P4-ATPases, which were previously not known to be expressed in rat hepatocytes at the protein level. P4-ATPases are important in maintain the lipid balance of hepatocyte membranes. Impairment of ATP11C leads in a mouse model to the accumulation of cholephilic compounds in the plasma. This finding demonstrates that P4-ATPases may be a class of proteins having an underestimated role in bile formation and consequently could also contribute to cholestatic liver disease.
Primary sclerosing cholangitis and IgG4-related sclerosing (autoimmune) cholangitis

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Primary sclerosing cholangitis (PSC) is a chronic and progressive disease of the biliary tree characterized by concentric, obliterative fibrosis leading to bile duct stricturing and eventually cirrhosis in the majority of cases. Although the underlying etiopathogenesis of PSC is unknown it is considered to be a condition of immune dysregulation in genetically predisposed patients interacting with a particular constitution of the biome. There is a strong association with the HLA system on chromosome 6, particularly with the HLA A1, B8, DR3 haplotype. Approximately three quarters of the Northern European PSC population have concomitant inflammatory bowel disease (IBD), with the predominant form of IBD being ulcerative colitis (UC). It is likely that PSC/IBD represents a distinct IBD phenotype. Unlike most immune-mediated conditions, PSC tends to affect men (male:female 2:1), some presenting with fatigue, right upper quadrant abdominal pain, weight loss, pruritus and intermittent jaundice. However, over half of the patients are asymptomatic at diagnosis.

Serum biochemical tests usually indicate a cholestasis and the diagnosis is established by cholangiography, usually magnetic resonance cholangiopancreatography (MRCP). Endoscopic retrograde cholangiopancreatography (ERCP) is reserved for when there is diagnostic doubt remaining after MRCP. PSC is a premalignant disease; and malignancy (hepatobiliary carcinoma and colonic malignancy in patients with IBD) has become the main cause of death. Approximately 1 in 10 of PSC patients will develop cholangiocarcinoma, with an annual incidence of 0.5–1.0% per annum.

The disease course is highly variable between individuals; most PSC patients reach the combined end-point of death or liver transplantation at a median time of 21 years following their diagnosis. Previously, prognostic models have been unsuccessful in predicting the natural history of an individual patient. Recent studies have shown that normalisation of serum alkaline phosphatase at one year after diagnosis to < 1.5 x the upper limit of the normal range is associated with excellent long term prognosis. There is no curative treatment for PSC. Unfortunately, no medical therapy has been proven to improve prognosis in PSC and the use of oral ursodeoxycholic acid is controversial. A number of new therapeutic agents are in clinical trials. Liver transplantation is the only therapeutic option with proven benefit for patients with advanced liver disease.

IgG4-related disease (IgG4-RD) is a rare, male predominant systemic disease, distinct from PSC, which may involve the pancreas (autoimmune pancreatitis type 1) and the biliary system (IgG4-related sclerosing cholangitis), in the majority of patients. The biliary changes may be indistinguishable from PSC on cholangiography. Many other organs may be involved including the salivary glands, lungs, kidneys and aorta.
It is characterized by an elevated serum IgG4 in three quarters of patients and an infiltration into the affected organ of lymphocytes staining positive for IgG4, together with associated storiform fibrosis. Unlike PSC, it is highly responsive to oral corticosteroid therapy which may result in complete reversal of the biliary stricturing. Relapse occurs in approximately half of the patients requiring long term immunosuppressant therapy.
Novel therapeutic options for primary biliary cholangitis and primary sclerosing cholangitis

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Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) represent two prototypic cholangiopathies with unknown etiology. Both diseases are currently seen as chronic immune-mediated liver diseases characterized by progressive cholestasis and loss of functional bile ducts, biliary type of liver fibrosis and both may lead to liver cirrhosis. Since there is a significant proportion of PBC patients with under-response to UDCA treatment and currently there is no proven effective medical treatment for PSC, there is obviously a need for novel therapeutic options. Recent advances in (i) understanding the regulation of bile acid synthesis and transport in liver and intestine together with identification of central regulatory proteins (e.g. FGF19), (ii) discovery and characterization of nuclear hormone receptor function (e.g. FXR, RXR, PPARs, and VDR) and their respective specific ligands, and (iii) some insights into the potential immunopathogenesis of these complex diseases yield numerous novel therapeutic concepts for cholangiopathies and led to drug developments currently at different stage of testing and position in the drug pipeline (e.g. FXR ligands, ASBT inhibitors, biologicals targeting receptors, integrins and ligands such as MAdCAM-1, VAP-1, α4β7, CCR9, CD20, IL-10, IL-8 and LOXL2, and side chain- modified bile acids such as norUDCA). This dynamic drug development underscores the importance of international study groups for PBC (The Global PBC Study Group) and PSC (IPSCSg) to coordinate clinical testing for more rapid progress and best benefit of our patients.
Session III

Non-alcoholic and alcoholic liver disease
Novel insights into the pathogenesis of NASH

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Enhanced fat uptake by hepatocytes in combination with a sedentary life style leads to non-alcoholic fatty liver disease (NAFLD), comprising a spectrum of liver disorders ranging from fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH) which can proceed to fibrosis, cirrhosis and HCC. Currently, 90 million Americans and 30 million Europeans suffer from NAFLD. At the same time there is no established pharmaceutical to treat NASH and established standard of care therapy for HCC is limited. A “two-hit hypothesis” has been proposed for NASH progression from NAFLD: Lipid accumulation in the cytoplasm of hepatocytes is considered the first step in NASH development; however, a second hit promoting oxidative stress, inflammation, DNA damage, hepatocyte cell death and fibrosis is needed. In C57BL/6 mice, NASH can be induced by methionine/choline-deficient diet (MCD) or choline-deficient diet (CD) but not by high fat diet (HFD) alone. However, C57BL/6 mice fed with MCD or CD do not develop obesity, metabolic syndrome or HCC and the diet has to be discontinued after a few months due to weight loss (up to 40%) or cachexia. Hence, these short-term approaches fail to recapitulate NASH-induced long-term consequences found in the human liver and possibly other metabolic organs. Deficiency of the essential nutrient choline was described in NAFLD patients to exacerbate NAFLD and NASH. Moreover, humans with insufficient choline-uptake have defects in hepatic lipoprotein secretion, oxidative damage caused by mitochondrial dysfunction and ER stress. We combined choline deficiency with a high fat diet (CD-HFD), which we hypothesized may lead to metabolic syndrome, steatosis, liver damage and NASH, thus delivering the “second hit” that promotes dietary-induced liver carcinogenesis – similar to the human situation. This approach enabled us to study a chronic mouse model of NASH in the context of metabolic syndrome, triggering subsequent HCC in C57BL/6 mice, in the absence of chemical carcinogens or genetic mutations predisposing to NASH or HCC development. CD-HFD fed mice display several pathologies for a long time frame: abdominal obesity, overweight, insulin resistance, liver damage, fibrosis, hepatic mitochondrial damage, dyslipidemia and NASH as observed in human patients. Moreover, HCC developed 12 months post CD-HFD start resembling human HCC. Using this mouse model we demonstrated that CD8+ T-cells and NKT-cells become activated during metabolic syndrome, interact with hepatocytes and alter hepatic lipid metabolism causing NASH and HCC. Here I will report on novels findings in regards to the use of this and other NASH models.
Emerging trends treatment of nonalcoholic steatohepatitis

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Nonalcoholic steatohepatitis (NASH) has emerged as a leading cause of liver-related morbidity and mortality. The therapeutic goals for NASH vary according to the underlying disease activity and fibrosis stage. In those with early stage (stage 1–3) disease, the goal is to decrease disease activity and prevent progression to cirrhosis. Actual regression of fibrosis is even more desirable than reduced rates of progression. For those with advanced stage i.e. cirrhosis, the goal is to reduce the rates of liver-related outcomes and/or actually produce regression from cirrhosis. Multiple agents are currently being considered in “bottom up” therapeutic trials focused on the underlying metabolic perturbations that drive cell stress and inflammation which eventually drive fibrotic remodeling of the liver. Many of these are insulin sensitizing agents such as PPAR-γ, PPAR-α, PPAR-α/γ and PPAR-α/δ agonists. The largest and best quality data exist for thiazolidinediones such as pioglitazone a PPAR-γ agonist. They reduce steatosis, inflammation and ballooning and there is a suggestion based on meta-analysis of the trials that they reduce fibrosis as well. A recent trial with a PPAR-α/δ agonist elafibrinor demonstrated a remarkable improvement in cardiometabolic parameters but failed to demonstrate any significant improvement in a priori pre-defined liver endpoints. However, subsequent re-analysis using revised definitions of resolution of steatohepatitis and focusing on those with NASH with high disease activity and some hepatic fibrosis, it appeared to significantly improve liver histology. Saroglitazar is a PPAR-α/γ agonist which is approved for diabetes in India and is also moving in to pivotal trials for NASH. Another major class of compounds relate to FXR agonists. Obeticholic acid (OCA) has been shown to improve all components of early stage NASH but is associated with some increase in LDL-cholesterol whose clinical relevance remains to be determined. Several new FXR agonists based on small molecules which are believed to improve NASH without increased LDL-cholesterol are in early phase trials. GLP-1 is emerging as another important target and liraglutide showed promising results in a very small pilot study. The role of DPP inhibitors and indirect GLP-1 agonists such as intestinal TGR5 agonists is in early phases of investigation. Anti-inflammatory targets with some metabolic effects such as n3 PUFAs did not show any benefit in current trials but may have failed due to under-dosing. There are also early phase efforts targeting cell death using anti-caspase agents. Cenicriviroc a CCR2-CCR5 antagonist targets the disease at the interface of inflammation and fibrosis. Initial data from a phase 2B trial shows promising results with an antifibrotic effects. A major effort to take a “top down” approach with direct anti-fibrotic therapy with a lysl-oxidase antibody and a saccharide that binds and clears galectin are under way. CTGF-based therapeutics are under development.
Role of genetic factors in non-alcoholic and alcoholic liver disease

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Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) related to the metabolic syndrome are among the commonest causes of advanced liver disease in affluent societies. The susceptibility to develop significant liver disease in either entity is determined by a number of constitutional, environmental and genetic factors although the interplay between them remains unclear. Interestingly, besides presenting with similar clinical and histological features, both diseases share astonishing parallel natural histories showing progression from steatosis, to steatohepatitis and fibrosis/cirrhosis, and eventually hepatoma. The heritability of both ALD and NAFLD, and particularly progression of either, is well documented and often overlaps in a given patient.

The quest for robust genetic modifiers that govern evolution and progression of ALD and NAFLD has been remarkably successful after years of stagnation, and mutually fostering. Genome-wide scans in sufficiently high numbers of patients with NAFLD have identified the first genetic risk locus for steatosis, steatohepatitis, fibrosis and even hepatoma, and was later also confirmed to associate with similar phenotypes in ALD. For ALD, three strong candidate genes which confer risk, *PNPLA3*, *TM6SF2* and *MBOAT7*, have been identified. In turn, *TM6SF2* and *MBOAT7* were also found to confer risk for NAFLD progression. How these variants confer risk and the nature of any functional interplay between them remains to be determined. This information will undoubtedly increase our understanding of the pathophysiology of metabolic liver disease, and perhaps other chronic liver diseases. Likewise the way in which this genetic information should be used in clinical practice has yet to be determined and tested but it will likely influence patient management.
Acute alcoholic hepatitis (now called alcoholic hepatitis, AH) manifests as a clinical syndrome characterized by recent jaundice and liver function deterioration in an active drinker patient. The principal cause of AH is alcoholic steatohepatitis (ASH) defined histologically by the coexistence of steatosis, hepatocyte ballooning and satellitosis. While non-severe AH usually responds to alcohol abstinence, severe AH, identified by Maddrey scoring ≥ 32, has a bad prognosis and is traditionally treated by a 28-day course of prednisone therapy. A recent trial, which showed no improvement of long term survival but significant reduced mortality after 28 days of corticoid therapy compared to placebo or to pentoxifylline treatment, however opens a debate on its efficacy. This trial has to be interpreted with caution given the high rate of alcohol recidivism and no histological confirmation of ASH. N-acetyl-cysteine supplementation combined to steroid therapy is also able to reduce the 28-day mortality compared to steroid alone. While guidelines from nutrition societies recommend high calorie intake and protein supplementation in decompensated liver diseases, intensive enteral nutrition through a nasogastric tube together with corticoid treatment does not reduce mortality compared to corticoid alone in a recent study with ASH patients. Stimulation of liver regeneration through interleukin 22 or granulocyte colony stimulating factor administration, inhibition of apoptosis or oxidative stress, early liver transplantation and modulation of systemic inflammation and gut microbiota through prebiotic, antibiotic or fecal transplantation approaches constitute new therapeutic perspectives that are investigated in current clinical trials. For long term survival, strategies for persistent alcohol abstinence remain the key of success, opening another large research field.
Session IV

Environmental triggers in inflammatory bowel diseases: What is evident?
Antibiotics: Do they cause later onset IBD?

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If changes in the diversity of the gut microbiome or in specific gut microbiome species are replicated and found to be highly associated with IBD then it must also be explained how these gut microbiome changes emerge. Despite years of investigation, to date no single microbial infection has been shown dominate the gut microbiome in persons with IBD the way toxigenic clostridium difficile, for example, triggers pseudo-membranous colitis. Antibiotics can alter the gut microbiome which not only can facilitate the emergence of clostridium difficile, but also can change the relative abundance of various species. These changes may last for long after discontinuation of the antibiotics. In this lecture I will discuss what evidence is available that antibiotic use can trigger IBD. An important factor to consider is the timing of antibiotic ingestion in relation to gut microbiome development and whether the evidence is different in children versus adults with IBD. If antibiotic use is proven to be a critical factor in the emergence of an “IBD-prone” gut microbiome then it is important that the epidemiology of antibiotic use worldwide fits with the emergence of IBD worldwide.
The gut microbiota: Dysbiosis or infection?

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In the setting of enormous numbers of microbes in the intestinal tract, avoidance of frank inflammation requires adaptation both on the side of the microbiota and the side of the host. Different elements of the intestinal microbiota shape their gene expression profiles and their replication rates to the niche in which they are currently resident – both longitudinally and transversely in the GI tract. This means that even members of the same microbial species behave in a very different way according to their niche – a further level of complexity is added in terms of gene expression and metabolism according to the composition of microbes that also form the consortium within the niche.

On the side of the host, exposure to the microbiota entails adaptation of all cellular elements of the intestinal structure. This starts even before birth through the exposure of microbial molecules that penetrate the maternal and fetal circulations from the mother’s own microbiota. Molecular exposure of intestinal and systemic tissues to the products of an endogenous colonization is limited through the ability to induce innate immune mechanisms, secretory antibodies and metabolism of xenobiotics. My talk will use murine genetic strain combination methods in combination with gnotobiology to illustrate the different mechanisms involved at a molecular level.
Breast feeding, air pollution, NSAIDs: Do they cause IBD?

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Crohn’s disease (CD) and ulcerative colitis (UC) (inflammatory bowel diseases; IBD) are chronic immune-mediated diseases associated with considerable morbidity by virtue of their young age at onset and protracted relapsing course. While the exact cause is unknown, a dysregulated immune response to commensal intestinal flora appears to be key in the development of these diseases. While genetics is a strong risk factor for both CD and UC, it insufficiently explains the variance in disease risk and does not account for temporal and geographic trends in disease incidence. Thus, environmental influences appear to play an important role in the pathogenesis of IBD. Several studies have confirmed an inverse association between being breastfed in infancy and reduced risk of both CD and UC. This effect may be mediated through the effect of breast milk on the gut microbiome, prevention of infections in infancy, and development of oral tolerance. The rising incidence of IBD in countries witnessing rapid industrialization and urbanization suggests that one possible contributing factor could be air pollution. While there is limited epidemiologic evidence in support of this hypothesis, laboratory studies support plausibility through induction of systemic and intestinal inflammation. Distinct from their well-recognized effect in causing gastric and duodenal ulcerations, NSAIDs are associated with an increased risk of incident CD and UC and may trigger relapses in up to a third of users, exerting their effects through a panoply of possible mechanisms. Further research into environmental influences and their mechanisms of influence may improve our understanding of the etiopathogenesis of inflammatory bowel diseases.
Environmental factors and their disease-modifying potential are increasingly recognized in the pathogenesis of inflammatory bowel disease. This is largely driven by the perception that the prevalence and incidence of IBD are on the rise within the last few years, especially in non-western countries. A possible factor that is believed to be of importance is hypoxia. The role of hypoxia as a modifying and even as a causative factor in the genesis and maintenance of inflammation has been increasingly elucidated in recent years. Hypoxia is believed to be a main inducing factor of inflammation. This has been studied in different animal experiments as well as in humans exposed to hypoxia. In several studies -mainly in mice- animals exposed to short-term hypoxia accumulated inflammatory cells in multiple organs and showed elevated cytokines in the blood. Comparable studies were performed in humans, mainly in healthy mountaineers. We reported on the association between IBD flare-up episodes and journeys to high-altitude region and aircraft travels. According to these findings we concluded that flights and stays at high altitudes > 2000 mg are a risk factor for increased disease activity in IBD. To evaluate the potential influence of hypoxia on the course of IBD on a biomolecular level and to test the effects of hypoxia under standardized conditions, we finished a prospective and controlled investigation in both healthy controls and IBD patients in stable remission. The study participants underwent a 3 hours exposure to hypoxic conditions simulating an altitude of 4000 meters above sea level in a hyperbaric pressure chamber and clinical parameters as well as blood and stool samples were collected at several time points.
How to translate environmental factors into mechanisms of IBD?

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Inflammatory Bowel Diseases (IBD) are multifactorial diseases resulting from complex interactions between different immune cells, alterations in the vascular endothelium, changes in the tight junctions of colonic epithelial cells and deregulation of the gut microbiome. Genome-wide association studies (GWAS) have identified 163 IBD susceptibility gene loci, however very few SNPs correspond to coding variation with a clear effect on protein function, while the majority of these SNPs are located in epigenetically-regulated areas. Thus, genetic factors account only for a small portion of the overall disease variance, indicating a need to better explore gene-environment interactions in IBD pathogenesis. Epigenetic factors act as mediators between the environment and the genome, regulating the inflammatory response. The human IBD epigenome harbors alterations both at the level of DNA methylation and histone tail modifications. DNA methyltransferase 1 (DNMT1) and 3 (DNMT3) are the enzymes involved in the DNA methylation process and have been found to be up-regulated in colonic tissues from IBD patients. Furthermore, the presence of IBD-associated SNPs in enhancer areas suggests the importance of the characterization of histone modifications in IBD patients. Here, we will discuss the state-of-the-art high throughput technologies, such as the Reduced Representation Bisulfate Sequencing (RRBS) and Fixed Tissue-ChIP-Sequencing (FiT-ChIP-Seq), to study the human IBD Epigenome. In addition, we will examine the computational models that could be used to integrate the IBD Epigenome with other IBD “omics” data in order to construct and visualize the IBD interactome. Importantly, the identification of the IBD interactome could allow us to identify novel drugs targeting the IBD interactome following an approach named “Network-based Chemical Screening” (NCS). This strategy could lead to the construction of an IBD Drug-Interactome Map. Here, we will present a novel chemical compound that regulates the IBD Epigenome and is effective on suppressing development of colitis in mice. Taken together, we propose that characterization of the IBD Epigenome could contribute to our understanding of IBD pathogenesis, resulting in the development of IBD personalized therapeutics.
New treatment options in IBD based on new insights into disease pathophysiology

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Treatment options for IBD have evolved for at least 80 years, transitioning from the empirical anti-inflammatory drugs of the early 1940’s to the sophisticated biological therapies of the 2000’s. Early therapies, such as sulfasalazine and corticosteroids, were aimed at controlling inflammation as a whole, while subsequent therapies aimed at more specific effects, such as immunosuppression with azathioprine or methotrexate, followed by agents targeting specific pro-inflammatory molecules. While most practitioners still take advantage of both old and new drugs as dictated by the clinical situation, there is an increasing trend of using drugs that are rationally developed based on the newest insights into IBD pathophysiology. Following this tendency treatments should intervene on the components of IBD pathogenesis: the exposome (the environment), the genome, the gut microbiome and the immunome. This approach is logical, but not necessarily applicable to all components because of practical, ethical and logistic reasons. The challenges imposed by trying to modify the exposome are daunting, but we can modify the diet, change or eliminate IBD-risk associated medications, such as contraceptives, and recommend no smoking. However, before being able to effectively modify the patient environment, much greater knowledge must be acquired of what the exposome is all about and what in it should be altered. Genetic therapy is becoming increasingly realistic with advanced technique such as gene deletion and replacement with the CRISPR/Cas9 system, but at the moment this is not ethically doable. In addition, targeting gene variants alone is highly unlikely to offer any significant therapeutic benefits considering that IBD-associated variants are also present in healthy people, and multiple variants should be targeted in any single patient. Attempts to modify the gut microbiome with antibiotics, probiotics and prebiotics have been going on for several decades and therapeutic efficacy can be observed in some situations. With the explosion of studies and a great expansion of knowledge of the gut microbiome new therapies have emerged such as fecal transplantation. So far results are variable and inconsistent, but various important lessons have been learned: not all IBD patients benefit, not all donors generate “therapeutic stools”, and changes in the recipient microbiota is only transient. Clearly more knowledge is necessary before modifying the microbiome will be consistently beneficial. The immunome is where the most striking advances have occurred in the last 15 years. The discovery of cytokines and characterizing their function has allowed successfully blocking pro-inflammatory cytokines like TNF-α, IL-6 and IL-12, and securing marked clinical improvements. Discovery of immunocyte homing patterns and the respective receptors has allowed preventing or limiting accumulation of immune cells in the inflamed mucosa with good clinical results. Understanding the pathways triggered by cell activation permits now to block specific signaling molecules with clear
clinical benefits, as in the case of JAK inhibitors. Despite this string of successes, management of IBD is still suboptimal because it fails to offer a true “personalized therapy” targeting specific pro-inflammatory molecules in individual patients. IBD is a prototypical complex disease, and each patient develops gut inflammation due to a unique combination of environmental, genetic, microbial and immune factors. Complex diseases require complex therapies addressing not one, but a multitude of pathogenic factors. The tools to define such discrete combinations of factors are becoming available, and the next decade will witness even greater and more successful results with the broad adoption of systems biology and bioinformatics tools.
Session V

Treatment decisions: Where is the place of new compounds in IBD treatment?
Anti-integrins: Where is the place in CD and UC treatment algorithms

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The anti-integrin class of antibody drugs has already been populated with two agents that have concluded their phase III program, natalizumab and vedolizumab. Natalizumab binds the \( \alpha 4 \beta 1 \) and \( \alpha 4 \beta 7 \) integrin whereas vedolizumab shows exclusive binding to \( \alpha 4 \beta 7 \) integrin. Etrolizumab, an antibody targeting \( \beta 7 \) integrin and hence blocking both \( \alpha 4 \beta 7 \) and \( \alpha E \beta 7 \) integrin is still examined in a large series of phase III studies. Oral approaches that target \( \alpha 4 \) integrin either by chemical entities or through small polypeptides are in early phases of clinical development.

Natalizumab has shown undoubtedly efficacy in both naive and TNF refractory Crohn’s disease. It has shown a strong steroid sparing effect and excellent maintenance capability which appears to be typical for the class. However the broad spectrum of binding including \( \alpha 4 \beta 1 \) integrin (that was targeted to extend the profile of the antibody for the therapy for multiple sclerosis) has given rise to reactivation of JC virus which is the cause for PML, a devastating encephalitis, in about 1/1000 patient years. This drug has therefore not found any use in Crohn’s disease and is approved in the USA only on a named patient base. It is, however, widely used for the therapy of multiple sclerosis.

The development story of vedolizumab is unlike more successful. After a predecessor compound, MLN-02 showed efficacy in ulcerative colitis the antibody was redesigned for avoidance of immunogenicity. It then showed in large phase III trials efficacy in both Crohn’s disease and ulcerative colitis with regards to induction, maintenance and steroid reduction. Real world data that has been consolidated by meta-analysis confirms the efficacy in both Crohn’s disease and ulcerative colitis. The side effect profile is remarkably benign with almost no drug related severe side effects that were reported.

Vedolizumab is the choice of drug if anti-TNF has been exhausted and if a slow onset of efficacy over 6 to 10 weeks can be tolerated. Another option in these patients will be ustekinumab when the drug becomes available. In the choice of the primary biologic agent the efficacy profiles, side effect risks and the costs of anti-TNF therapy and vedolizumab have to be carefully weighted in an individual decision for the patient.
Anti-IL12, anti-IL23, anti p19 and JAK inhibitors: Where do we stand?

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There are still considerable unmet needs in the targeted treatment of inflammatory bowel disease despite the availability of several anti-TNF agents and integrin inhibitors. Ustekinumab, the anti-IL-12/anti-IL-23 p40 inhibitor has been shown to be effective in the induction and maintenance treatment of biologic therapy therapy naïve as well anti-TNF failure Crohn disease patients. Ustekinumab appears to be well tolerated with a low risk of infection. Ustekinumab has a long half-life and is administered as a loading intravenous dose, followed by subcutaneous maintenance dosing. Ustekinumab therefore appears to offer a new option in the therapy of both anti-TNF naïve and anti-TNF failed Crohn disease patients. There is already considerable experience in using off-label ustekinumab in Crohn disease. If only IL-23 is targeted via blockage of p19 subunit, the initial results appear promising in Crohn disease, even though the majority of patients had failed biologic therapies. Risankizumab has now entered phase 3 trials to confirm efficacy in Crohn disease. In ulcerative colitis, the oral JAK1/3 inhibitor tofacitinib has shown efficacy in inducing remission in ulcerative colitis patients. As the first oral targeted therapy in inflammatory bowel disease, tofacitinib may offer novel strategies of therapy in ulcerative colitis.

With the introduction of several new classes of drugs, it is now imperative that we find ways of stratification of inflammatory bowel disease to determine which patient subgroups may respond best to which classes of targeted therapies. This will take complex studies in large cohorts of patients.
Therapy of ulcerative colitis with phosphatidylcholine: Underlying concept and clinical efficacy

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Objective: The intestinal mucus forms a hydrophobic barrier against colonic microbiota; a defective mucosal barrier has been suggested as an underlying cause of ulcerative colitis (UC). Phosphatidylcholine (PC) is the most abundant phospholipid in intestinal mucus, indicative for a specific transport system across the mucosal epithelium to the intestinal lumen. We propose that the key pathogenetic feature of UC is an intrinsically low (70% reduced) mucus PC content. What remains unclear is how PC accumulates in mucus under physiological conditions, and why it fails to do so in UC and induces an inflammatory phenotype. Based on the discovered underlying concept, the efficacy of topical application of PC to the colon was clinically evaluated.

Results: In a transwell tissue culture system with the polarized intestinal tumor cell line CaCo2 it was shown that PC could not substantially be internalized by the cells. However, after basal application of increasing PC concentrations, an apical transport of 47.1 ± 6.3 nmol h⁻¹ mM PC⁻¹ was observed. Equilibrium distribution studies with PC applied in equal concentrations to the basal and apical compartments showed a 1.5-fold accumulation on the expense of basal PC. Disruption of tight junctions (TJ) by acetaldehyde or PPARγ inhibitors or by treatment with siRNA to TJ proteins suppressed paracellular transport by at least 50%. Transport was specific for the choline containing the phospholipids PC, lysoPC and sphingomyelin. We showed that translocation is driven by an electrochemical gradient generated by apical accumulation of Cl⁻ and HCO₃⁻ through CFTR. Pretreatment with siRNA to mucin 3 which anchors in the apical plasma membrane of mucosal cells inhibited the final step of luminal PC secretion. PC accumulates in intestinal mucus using a paracellular, apically directed transport route across TJs. To prove the hypothesis that disruption of lateral TJ causes diminished luminal PC transport and induces an UC phenotype, we examined adult C57BL6 wildtype and newly generated mutated mice with tamoxifen inducible villin-Cre dependent intestinal deletion of kindlin1 and 2 which were assumed to present with disrupted lateral TJ. Electron microscopy of mucosal biopsies of both mutants revealed indeed loosening of lateral TJ with expansion of the mucosal crypt lumina. PC secretion into mucus was reduced by >65% and the mucus PC content dropped from 80 in controls to 39 and 27 nmol · mg mucin⁻¹ in kindlin1 and 2⁻/⁻ mice, respectively. In parallel the hydrophobicity was reduced revealing a contact angle reduction from 72° in controls to 30° and 35° in kindlin1 and 2⁻/⁻ mice, respectively. Accordingly microbiota penetrated into the submucosa. Later on, a full blown intestinal inflammation was present in both mutants with loose bloody stools as well as macroscopic and histologic features of colitis. The inflammation could be reversed by oral PC supplementation. In analogy, colonic biopsies of patients with UC also showed TJ disruption revealing widened crypt luminal diameters and functionally an impaired luminal PC secretion, when compared to controls and Crohn's disease. This accounted for the low colonic mucus PC content and the reduction of hydrophobicity with a contact angle of 47° in UC. In 3 RCTs it was shown that topical PC supplementation with delayed release PC preparations resulted in compensation of the PC loss and in significant improvement of clinical activity, endoscopic appearance and life quality. This is currently being tested in two phase III trials.
**Conclusion:** A key pathogenetic feature of ulcerative colitis is a disturbance of newly described paracellular TJ mediated transport process of PC resulting in a low mucin associated mucus PC content and reduction of mucus hydrophobicity which enables microbiota invasion and mucosal inflammation. Recompensation of the mucus PC depletion re-establishes the mucosal barrier and hence shown to be an effective novel therapeutic strategy.
Paradoxical inflammation – A new phenomenon of biological therapy

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The use of biologics, in particular anti-tumor necrosis factor-alpha (anti-TNF) agents, for the treatment of inflammatory bowel diseases (IBD) has increased dramatically over the past 2 decades [1, 2]. Overall, these agents have demonstrated safety and efficacy when initiated and monitored appropriately in IBD populations. However, reports of autoimmune reactions such as skin lesions (psoriasis), vasculitis, demyelinating disorders or drug-induced lupus are increasing. These reactions have been described as “paradoxical inflammation,” as they occur in patients on an anti-TNF therapy [3, 4] which was initiated with the intent to treat an inflammatory condition such as rheumatoid arthritis or IBD. These reactions can be difficult to manage, and may result in discontinuation of an otherwise effective agent [5]. Skin lesions are the most common of these paradoxical complications, and can occur in up to 29% of patients on anti-TNF agents [6]. Management of these complications ranges from adding additional therapies (such as topical agents or immunomodulators) to discontinuation of the anti-TNF. In many instances, alternate therapies may be needed to control the paradoxical response, such as the initiation of ustekinumab, an interleukin (IL)12 and 23 inhibitor, to treat refractory paradoxical psoriaform skin lesions. This presentation discusses the incidence, risk factors and management of various paradoxical reactions in patients with IBD.

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Session VI

Some news about old friends
Methotrexate in ulcerative colitis

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In 1989 Kozarek et al. were the first to report a beneficial effect of intramuscular methotrexate (MTX) therapy in 21 patients with refractory Crohn’s disease (CD) or ulcerative colitis (UC) [1]. It took another 6 years to confirm clinical efficacy of MTX as induction regimen and 13 years as maintenance therapy in patients with CD. Two landmark trials of the North American Crohn’s Study Group Investigators published in 1995 and 2000 established that 25 mg MTX given intramuscularly once weekly for induction and 15 mg MTX given intramuscularly once weekly for maintenance was more effective than placebo in improving clinical symptoms and reducing requirements for prednisone [2, 3]. The further exploration of MTX in prospective clinical trials in UC was initially stalled in 1996 by the publication of a negative result of an Israeli multi-center study investigating the clinical efficacy of 12.5 mg MTX given orally in steroid dependent UC [4]. However, starting around the year 2000 MTX was effectively used in patients with UC in clinical practice as shown by numerous retrospective single center analyses [5]. The positive results of these retrospective findings triggered the development of 2 prospective clinical trials, one conducted by the GETAID (Groupe d’Étude Thérapeutique des Affections Inflammatoires du Tube Digestif) in France and one sponsored by the NIH (National Institute of Health) and performed by the CCFA – CRA (Crohn’s and Colitis Foundation of America – Clinical Research Alliance) in the USA. The French METEOR (Comparison of Methotrexate vs Placebo in Corticosteroid-dependent Ulcerative Colitis) trial investigated the clinical efficacy of subcutaneously applied MTX 25 mg once weekly as an induction regimen over 16 weeks. The trial failed to achieve the primary endpoint of a combined clinical and endoscopic remission, but showed a significant advantage of MTX to placebo for the secondary endpoint of clinical remission only [6]. Several factors might have contributed that the results of this investigator initiated trial are not as clear-cut as one would have hoped for [7]. MTX could represent a unique and affordable maintenance therapy for UC patients in need for an immunosuppressive treatment [8]. Currently another investigator initiated study evaluates the clinical value of MTX in UC, the US MERIT-UC trial (Methotrexate Response In Treatment of UC). The primary endpoint of this prospective, randomized, placebo controlled study is the efficacy of MTX to maintain steroid free remission over 54 weeks. This trial is still recruiting and the results are expected in early 2018.

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5-ASA: Topical, oral or both

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5-Aminosalicylic acid (5-ASA) is a multi-target compound. Since decades it serves as a standard therapy in IBD. Taken by mouth 5-ASA becomes rapidly acetylated in the intestinal mucosa. By this it is nearly completely absorbed in the most proximal parts of the small intestines. Circulating 5-ASA and its metabolites is easily excreted via the kidneys. The mode of action in IBD is on the mucosal side of the bowel, thus being a local (or topical) therapy anyway, which makes intravenous application of 5-ASA senseless.

Drugs of 5-ASA for treatment of IBD have to be protected from early absorption by sophisticated slow or sustained release preparations which are aimed to deliver the active compound more distally to the inflamed sites of IBD. Nevertheless, given orally all 5-ASA preparations will loose on their intestinal concentration as they travel through the bowels down to the rectum. This results in less therapeutic activity in distal IBD and in higher circulating 5-ASA (metabolites) with the risk of systemic adverse events.

Alternatively, 5-ASA can also be applied via the rectum which allows high therapeutic concentrations in the (distal) colon. It is therefore not a surprise that rectal 5-ASA is therapeutically superior over oral 5-ASA for proctosigmoiditis ulcerosa. An interesting question here is to which proximal point expands rectal 5-ASA. Several factors determine the spread of rectal 5-ASA such as volume, viscosity, continuity and severity of inflammation. Because those parameters may change in an individual patient during the course of the disease exact prediction of the spread of the drug is not possible. Therefore, it makes sense to combine oral and rectal application of 5-ASA. In fact, this kind of combination therapy has shown very good therapeutic effects for induction and maintenance therapy in ulcerative colitis and those benefits include also extended localizations of the disease.

Applications of 5-ASA uses several formulations, in case of oral ingestion tablets and granules, in case of rectal application enemas, foams and suppositories. It is important to ask the patient for his preference, particularly in rectal treatment, because otherwise the patient will not be able to retain applications via the rectum.

In summary, all therapeutic effects of 5-ASA are local requiring topical application either by mouth or via the rectum. Both routes have advantages and disadvantages which can be overcome by the use of a combination of both forms. From clinical trials there is convincing evidence that according to the localization of IBD, both oral and rectal formulations have significant therapeutic effects. In patients with extended disease combination treatment is of superior effectivity. Most interestingly, no relevant adverse effects of rectal application of 5-ASA are known.
Thiopurines: When and how?

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Thiopurines (azathioprine and mercaptopurine) are efficient maintenance therapies of IBD, able to maintain a complete clinical and anatomical remission in about one third of patients. However they are slow-acting molecules, they should be used for prolonged periods, and there are concerns regarding their long term tolerance, particularly myelosuppression and malignancy.

When thiopurines should be started in the era of biologics?
Severe and complicated IBD forms require anti-TNF therapies, whereas immunosuppressants are not required in about one third of Crohn’s disease patients and more than half of ulcerative colitis patients who will experience a mild disease course, without significant intestinal damage. Indications for monotherapy with thiopurines are thus limited to the intermediate cases, particularly chronic active disease, steroid-dependency, and intolerance or failure of other maintenance treatments as mesalamine in ulcerative colitis or Crohn’s colitis. In these patients, there is no need to start thiopurines early in the disease course provided there is no significant anatomical damage. Decision should be taken after months of clinical, biological, and anatomical surveillance. Thiopurines should then be maintained as monotherapy in patients who achieve a prolonged steroid-free clinical and anatomical remission. Other indications of thiopurines are prevention of post-operative recurrence particularly in smokers and combotherapy during the first months of administration of an anti-TNF agent.

How thiopurines should be prescribed?
Although many physicians adapt the dose to TPMT phenotyping, an empiric weight-based dosing (2.0–2.5 mg/kg/day for azathioprine and 1.0–1.5 mg/kg/day for mercaptopurine) is safe when given under close biological monitoring. Complete blood counts and liver tests should be controlled every week during the first month, then every two weeks during the next 2 months, and then every 3–4 months as myelotoxicity and hepatotoxicity may also develop as late complications. Measuring 6-TGN and 6-MMP metabolites in erythrocytes may be used to monitor therapeutic drug levels, patient’s compliance and risk of toxicity.
Anti-TNFs: Originators and biosimilars

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Monoclonal antibody biosimilars (MABS) represent a new challenge for all the stakeholders involved in the use of therapeutic monoclonal antibodies. The first biosimilar of infliximab, named CT-P13, fulfilled the comprehensive criteria requested for EMEA approval and is now on many markets. This MABS has been tested only in rheumatological indications prior to approval, but then granted a full extrapolation of indications by EMEA, for use in all the indications of the originator. This large approval still elicit some concerns. Indeed one can argue that the differences in treatment regimens and patient populations across specialties may affect the efficacy and safety profile of MABS as compared to the originator infliximab, especially in IBD. Phase IV studies are so far reassuring and large scale experience rapidly accumulates, especially in Nordic countries, after switching was made mandatory at large scale. The ongoing experience will also contribute to pharmacovigilance programs regarding the new compound and its production chain. These interrogations will repeat themselves if more biosimilars to one originator arrive on the market, which is very likely, especially for infliximab.

In addition, the entry of cheap MABS in the large field of immune-mediated inflammatory diseases (IMID) will probably affect the overall use of biologicals in these indications, far beyond the choice between MABS and originator. Indeed, the indication and use of other anti-TNFs and even of biologicals with other mechanisms of action may be affected. Indeed, the price pressure will push doctors to prefer this choice to other biological therapies, and third party payors may try to influence these drug choices as well.

All these changes demand that large pharmacovigilance registries are developed, to further secure the absence of meaningful differences among the MABS and the originator, as well as to identify early should a problem happen in the production chain of one of the products that will also be under price pressure. Indeed, this competition will induce increased number of manufacturing changes, each with a risk of introducing an unwanted alteration in the molecule or in its dissolving solution. This pharmacovigilance effort will be the effort of all the stakeholders, as technology will further evolve to produce biologicals in totally new ways.

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Conflict of Interest Statement:
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Session VII

New treatment goals for IBD therapy
Imaging-guided treatment – Which imaging should be used?

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A new era in the treatment of Crohn’s disease is emerging, moving from symptom-based treatment to a more targeted approach. The assessment of extent and severity of inflammatory bowel disease (IBD) is in nowadays crucial. Clinical symptoms alone are neither sensitive nor specific for assessment of lesion severity in IBD. The ideal imaging method should be noninvasive, radiation free, able to depict pathologies in the small intestinal mucosa, and able to assess the bowel wall and surrounding structures. Cross-sectional imaging techniques have a high accuracy for the assessment of mucosal lesions and are reliable alternatives to ileocolonoscopy. They have a potential role in evaluating drug efficacy and driving treatment decisions. Cross-sectional analysis in experienced hands can be used for follow-up of disease activity, extramural complications, and postsurgical recurrence, decreasing (or even replacing) the burden of endoscopy in IBD.

CT enterography (CTE) provides several advantages over traditional small-bowel follow-through examinations, namely assessment of a longer portion of the gastrointestinal tract, accurate evaluation of disease activity and detection of extraintestinal manifestations or complications. CTE is highly sensitive and specific for active small intestinal inflammation with similar sensitivity to MR enterography (MRE), but with better interobserver agreement and possibly image quality (improved spatial and contrast resolution). The common signs of active or inflammatory Crohn’s disease in CTE include bowel-wall thickening, increased mural enhancement, mural stratification (reflecting increased enhancement along the mucosal and serosal surface of the bowel with intervening bowel wall oedema), and haziness of the surrounding mesenteric fat. CTE was as good as balloon-assisted enteroscopy for the assessment of disease extension, activity, and severity of small-bowel disease in patients with Crohn’s disease. With regard to detecting abscesses, CTE performs better than ultrasonography (92% vs. 87%).

MRE is a minimally invasive, radiation free procedure with a low complication rate and with equal or better sensitivity and specificity than CTE. Considering the need for frequent re-evaluation of disease status in patients with IBD and fear of ionizing radiation, ultrasonography and MRE are becoming the preferred examinations over CTE. T2-signal intensity of the intestinal wall is directly related to the following: the degree of oedema in the submucosal layer, dilation of submucosal lymphatic vessels, and signs of mucosal inflammation and ulcers. The two signals that best predict acute inflammation are wall (mural) thickness and T2 mural signal. Other MRE signs of active disease include mucosal hyperenhancement, mural stratification with a prominent vasa recta (comb sign), and mesenteric fat stranding. MRE and CTE are equally accurate for the identification of extraintestinal complications. The same is true for stenotic disease with similar sensitivity (85% vs. 92%) and specificity rates (100% vs. 90%) for both techniques. In conclusion, CTE, and MRE identify mucosal, transmural and extramural inflammation, and thus might change the paradigm of symptom-driven treatment to inflammation-driven treatment of disease.
Discontinuation of biologic treatments in IBD

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Biologics, and specifically the anti-TNF antibodies, have transformed and revolutionized the treatment of patients with inflammatory bowel disease (IBD). However, these therapies are costly and they do carry some risks that should be balanced with their clinical benefit when contemplating the duration of therapy. These considerations have served as a driver for exploring strategies to discontinue these drugs in patients with prolonged remission in whom this approach may be safely accomplished. From multiple cohort studies, it appears the overall risk of relapse after stopping an anti-TNF in Crohn’s disease and ulcerative colitis patients is roughly 40% at 12 months after therapy cessation. Factors predicting risk for relapse were extensively sought in order to identify patients in whom stopping the biologic may be best avoided. Despite methodological differences across studies, it appears that patients without deep remission (i.e. patients with endoscopic or biomarker evidence of inflammation) are at increased risk of relapse after stopping, as are those with high-adequate levels of anti-TNF before stopping. Preliminary evidence also suggest less post-withdrawal relapse in patients continuing an immunomodulator. In patients who relapse after anti-TNF cessation, re-treatment with the same biologic seems to re-induce clinical response in over 90% of patients, but this should be weighed against the small but finite risk of a severe flare that will culminate in the need for surgery. An algorithm is provided, outlining the decision tree for therapy discontinuation, including the need to consider alternative approaches such as withdrawal of the immunomodulator rather than the biologics, or implementing dose-reductions. Finally, it is yet unclear if such stopping strategies – exercised in infliximab and adalimumab treated patients – are also applicable for other anti-TNFs or for vedolizumab, for whom data in this respect are still lacking.
Long-term safety considerations for IBD therapies

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The treatment of inflammatory bowel disease has evolved over the course of the preceding several decades. Therapy now includes immunosuppressant medications targeting multiple different mechanisms that are used alone or in combination. This has resulted in substantial improvement in patients outcomes. However, chronic immunosuppression is associated with a number of potential adverse outcomes including serious and opportunistic infections, cancer and sometimes death. The choice of the most appropriate therapy depends on both the severity of the underlying illness, the likelihood that the selected medication will be effective for that patient, and the likelihood that the medication may cause harm to the patient. However, even knowledge of these three concepts would not be enough to make an informed decision without considering what the alternative therapy might be. This may include other medications in the same class, alternative classes of medications, the combination of multiple classes of medications, surgical therapies, and in some circumstances no therapy. In this review, I will discuss our current knowledge of the risk of serious adverse events chronic immunosuppression therapy for inflammatory bowel disease and provide a few practical tips on how to reduce the incidence and or consequences of these adverse outcomes.
Stem cell transplantation: The ASTIC trial and beyond

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Crohn’s disease (CD) is characterized by chronic inflammation in segments of the digestive tract and tissue damages. A significant progress has been made over the two last decades in the management of CD. However, a fraction of CD patients experiences severe disease, refractory to all available therapies. Autologous hematopoietic stem cell transplantation (HSCT) has been considered as an option for those patients. Other cell therapies using mesenchymal stem cells are in development.

Evidence for the feasibility and efficacy of HSCT has been reported in several types of severe treatment-resistant immune mediated inflammatory diseases, including multiple sclerosis and systemic sclerosis. Analyses of the EBMT database provided evidence for the feasibility and the toxicity of the HSCT procedures in immune mediated diseases. Despite long-term benefits, it is associated with a high morbidity and 2–10% mortality rate, making it an acceptable option for only highly refractory patients. The effect of HSCT on the disease is probably associated with a resetting of specific immune responses.

The first evidence of effectiveness of HSCT in IBD was observed in patients who underwent allogeneic or autologous HSCT for hematological or solid malignancy. The ASTIC trial, an international investigator-initiated randomized study, evaluated the early and late effects of autologous unselected HSCT on CD over 5 years. All cases suitable for the trial were discussed by a steering committee, which made suggestions for alternative management in a significant proportion of cases. We recently reported the outcome at one year. Forty-eight patients underwent mobilization of stem cells, and 45 patients were randomized to transplantation at one month (n = 23) or one year after (control arm, n = 22). Few patients in either arm achieved the primary endpoint of sustained disease regression (clinical remission off immunosuppressive drugs for 3 months with no evidence of intestinal inflammation on endoscopy and radiology). However, more HSCT patients were able to come off all immunosuppressive therapy than control patients and there was a clear trend for more HSCT patients being in clinical remission and free of active disease (endoscopy and imaging). HSCT was associated with a high number of adverse and serious adverse events, and one patient died after the start of conditioning.

The team of Barcelona recently published their experience on HSCT. Toxicity and complications during the procedure and within the first year following transplantation were reported. Viral infections were the most commonly observed complications, and one patient died due to systemic cytomegalovirus infection. Interestingly, changes in supportive care over the study, including antibiotic prophylaxis, and a reduction in cyclophosphamide dose, diminished the incidence of severe complications.

According to the EBMT guidelines, HSCT should be proposed only in patients with active CD refractory to immunosuppressants and biologics, and after consideration of all therapeutic options including surgery; and performed only in highly experienced centers.
Recently, a randomized clinical trial assessed the efficacy of allogeneic, expanded, adipose-derived stem cells (Cx601) for the treatment of refractory complex perianal fistulas in CD. A significantly greater proportion of patients treated with Cx601 versus placebo achieved remission.

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Down-regulation and gender discrepancy in the expression of programmed death 1 (PD-1) receptor and its ligand PD-L1 on peripheral T cell subsets in patients with alcoholic liver disease

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Introduction: Inflammatory cascade play a central role in the pathogenesis of alcoholic liver disease (ALD). Recently, two immune checkpoints, the programmed death 1 (PD-1) receptor and its major ligand PD-L1, have emerged as critical targets for immune activity modulation. Therefore, we aimed to explore their expression on peripheral T and B cell subsets in patients (pts) with ALD. Possible sex differences in immune response were also analyzed.

Methods: 33 naïve pts (14 females, 19 males) with ALD were prospectively recruited and compared with 21 age- and sex-matched healthy controls (HC) (8 females, 13 males). Pts were divided into subgroups based on their gender and severity of liver dysfunction. The expression of PD1 and PD-L1 on T CD3, CD4, CD8, and B CD19 cell subsets was analyzed by a FACSCalibur flow cytometer (Becton Dickinson, USA) with CellQuest software.

Results: Female controls expressed significantly lower PD1 levels on T CD3 cells in comparison with males (16.9% vs. 27.6%, p = 0.04), but there were no differences in PD1 and PD-L1 expression between females with ALD and controls. In males, significantly lower levels of PD1 expression on CD3 (median 17.7% vs. 27.6%, p = 0.02), as well as PD-L1 on CD3 (0.7% vs. 1.4%, p = 0.04), CD4 (0.7% vs. 1.6%, p = 0.03) and CD8 (0.4% vs. 1.1%, p = 0.02) were found in ALD group. No differences in PD1 and PD-L1 expression between different Child-Pugh subgroups were detected.

Discussion/Conclusion: Down-regulation of the PD-1 and PD-L1 expression on T cell subsets may contribute to aggravation of immune responses in ALD. Gender discrepancy in the PD1/PD-L1 signaling might have an impact on different sex susceptibility to toxic liver injury. It is reasonable to consider the PD-1/PD-L1 pathway as a therapeutic target in ALD treatment.
Branched-chain amino acid metabolism in Belarusian patients with alcoholic liver cirrhosis

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Introduction: The three branched-chain amino acids (BCAAs), leucine, isoleucine and valine, are among the nine essential amino acids for humans. Recent studies have revealed their functions. BCAAs have been shown to affect gene expression, protein metabolism, apoptosis and regeneration of hepatocytes, and insulin resistance. They have also been shown to inhibit the proliferation of liver cancer cells in vitro, and are essential for lymphocyte proliferation and dendritic cell maturation. In patients with advanced chronic liver disease, BCAA concentrations are low and may be closely associated with hepatic encephalopathy, malnutrition and the prognosis of these patients.

The aim of this study was to evaluate the level of leucine, isoleucine and valine in hospitalized Belarusian patients with alcoholic liver cirrhosis (ALC) compared with healthy subjects and in ALC groups depending on malnutrition severity.

Methods: BCAAs serum concentrations were detected by high-performance liquid chromatography in 30 healthy subjects and 73 patients with ALC (41 men, 32 women, median age 53 years, Child-Pugh class A [9.6%], B [61.6%], C [28.8%], severe malnutrition [54.8%]).

Results: Significantly reduced level of 2 BCAAs was found in the ALC patients compared with healthy subjects: valine (58/73; 78.3%, $T = 2071.0$, $p < 0.001$) and isoleucine (42/73; 56.8%, $T = 1886.0$, $p = 0.026$); 20.3% ALC patients had the increased level of both amino acid; serum leucine deviation haven't been revealed. Analysis of serum BCAAs depending on malnutrition severity showed only significantly reduced valine concentration in malnourished ALC patients ($T = 1399.0$, $p = 0.05$).

Discussion/Conclusion: ALC patients have lower isoleucine and valine blood concentrations compared to healthy subjects and lower valine in malnourished group compared to ALC patients with mild disorder of the nutritional status.
TGF-β1 -509C/T and IL-10 -1080A/G gene polymorphisms and tumor-infiltrating DCs

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Introduction: The association between carcinogenesis, gene polymorphisms and antitumor immunity conditions is well established. A great deal of cellular and molecular factors participate in the development and progression of colorectal cancer (CRC). The aim of our study was to investigate the relation between TGF-β1 -509C/T and IL-10 -1080A/G gene polymorphisms and tumor-infiltrating DCs in a group of Bulgarian CRC patients.

Methods: A total of 148 CRC patients and 176 controls from the Bulgarian population were genotyped for the -509C/T TGF-β1 and -1080A/G IL-10 polymorphisms via the RFLP-PCR method. Immunohistochemistry was performed with antibodies against CD1a, CD11c, CD123 and CD83 on paraffin embedded tissue.

Results: After genotyping for TGF-β1 -509 SNP was performed we found a statistically significant case-control difference in genotype frequency (p = 0.044, χ² test). It appeared that the carriers of TT genotype have 2.74-fold lower risk for CRC than those homozygous of the common allele C (CC) (OR = 0.365, 95% CI: 0.15–0.88; p = 0.015). We also found that the TT genotype carriers have the shortest median survival (14.4 months), followed by CT carriers (33.1 months) and CC carriers (54.3 months), (p = 0.045). Genotyping for the IL-10 -1080 SNP revealed a tendency that AA individuals had shorter survival compared to AG and GG (p = 0.196). Immunohistochemistry results showed that patients with CC genotype of TGF-β1 SNP showed lower cellular density of CD11c in the invasive margin of the tumor compared to those with CT and CC genotype (p = 0.033), while there was an opposite finding for CD83 + DCs in the invasive margin (p = 0.037). With regard to the -1080 IL-10 SNP we found that the carriers of at least A-allele have lower density of CD83 + DCs (p = 0.046).

Discussion/Conclusion: Our results showed that CT and CC genotypes of the TGF-β1 gene correlated with CD11c and suggest that this correlation is involved in the development of an inhibitory phenotype and tolerogenicity.
Crohn’s and Ulcerative Colitis Questionnaire-8 (CUCQ-8), a valid and quick quality of life measure in IBD

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Introduction: Most of the disease-specific quality of life (QoL) measures for inflammatory bowel disease (IBD) are lengthy and time consuming. None has been established for routine use in clinical practice. We designed this study to develop a short QoL measure in IBD.

Methods: A 32-item questionnaire, the Crohn’s and Ulcerative Colitis Questionnaire-32 (CUCQ-32) was developed by reviewing the literature and consultation with patients and experts. Construct validity was carried out using the Short Form 12 (SF-12) and the EuroQol 5 Dimensions (EQ5D) questionnaires and two disease severity measures (Simple Clinical Colitis Activity Index [SCCAI] and the Harvey-Bradshaw Index [HBI]. Test-retest analysis was done by asking patients to complete the CUCQ questionnaire twice in a period of two weeks.

Results: Data were obtained from 205 patients with IBD who completed the CUCQ-32. Psychometric analysis showed that Cronbach’s α was 0.88, item-total correlations were good and there was no ceiling or floor effects. Stepwise regression identified 8 items that accounted for more than 95% of the variance in the CUCQ-32. The resulting CUCQ-8 demonstrated good internal consistency (Cronbach’s α = 0.84); had good reproducibility (intra-class correlation coefficient = 0.94); was well correlated with the EQ5D (r = 0.58), the Short Form-12 (r = 0.65 for physical component and r = 0.63 for mental component); was responsive to change (responsiveness ratio was 0.64, p value < 0.05).

Discussion/Conclusion: CUCQ-8 is a short questionnaire, which has the potential to be an efficient tool for assessing the QoL of all patients with IBD in clinical practice.
Consenting patients for oesophagogastroduodenoscopy (OGD)

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Introduction: Informed consent is central to the relationship between all Health Professionals and their patients. There are no satisfactory data for the UK but in a review of 31 claims against endoscopists in England and Wales it appeared that in at least 12 instances patients consented to the procedure after little or no explanation. The aim of this study was to ensure valid consent is taken from patients having oesophagogastroduodenoscopy (OGD) in compliance with the Guidance.

Methods: Over 6 month period, data was gathered retrospectively on 62 patients (age range 24–93 years) who had OGD. The standards were: has the consent form specified the type of the procedure, was the writing legible, were medical terms used, was the procedure explained in lay man language, was this clearly documented, and has the consent form been filed in the case notes.

Results: Results showed that majority of the consent forms (84–87%) were legible and clearly specified the type of the procedure. However, only 45% of the consent forms were written in lay man words and medical abbreviations were used in 42% of them. Although 90% of the consent forms were filed in the case notes, only 13% of the consents were documented in the case notes.

Discussion/Conclusion: Out of the 62 consent forms studied, 13% did not specify the type of the procedure and many of them were written in medical terms. There was lack of documentation in the case notes that consent has been given by patient and required information was provided.
Development and validation of a new disease severity index: The Inflammatory Bowel Disease index (IBDex®)

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Introduction: A number of clinical indices have been put forward using different parameters based on different principles. However, none of these clinical indices have been properly validated using a robust methodology. Our aim was to develop, validate and apply a generic clinical severity index applicable to all adult patients with IBD.

Methods: A review of the literature and an expert focus group consultation were carried out in order to draw out relevant items from existing literature. The new index was called the Inflammatory Bowel Disease index (IBDex®). Standard psychometric analysis was carried out. The construct validity was assessed against biochemical markers, clinical and endoscopic indices. The new index was completed again within 6 weeks in to check responsiveness and reproducibility.

Results: IBDex® was used to assess 255 IBD adult patients (125 with Crohn's disease and 130 with ulcerative colitis), and 64 patients were re-evaluated within 6 weeks. It had good internal consistency (Cronbach’s α = 0.79) and correlated very well with Harvey Bradshaw Index (r = 0.94), the Simple Clinical Colitis Activity Index (r = 0.92), the Mayo Clinic index (r = 0.87) and the Simple Endoscopic Score (r = 0.76) all with p values < 0.05. IBDex® had a moderate but positive correlation with C reactive protein (r = 0.51) and erythrocyte sedimentation rate (r = 0.36) p values both < 0.05. The test-retest reliability was good (intra-class correlation coefficient 0.97) and responsiveness ratio was 2.27.

Discussion/Conclusion: IBDex® is the first properly validated clinical disease severity index in IBD. Our results showed that it is valid, reliable and reproducible and has the potential to be used in clinical practice.
Influence of steatosis on the activity of enzymes of mitochondrial electron transport chain of rat hepatocytes

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Introduction: Steatosis or non-alcoholic fatty liver disease (NAFLD) is considered one of the most common forms of chronic liver disease for today. Among main factors of steatosis are the disruption of diet and physical inactivity. The role of electron transport chain (ETC) complexes in mitochondrial dysfunction under conditions of steatosis is not clear. The aim of this work is to determine changes of the enzymatic activity of mitochondrial ETC complexes of rat hepatocytes under different types of steatosis.

Methods: The experiments were performed on 20 male Wistar rats. It was performed 2 series of experiments; each of them included 10 rats. In each series were control and research group. In the first series steatosis was caused by keeping on high-caloric diet (HCD) # C11024 for 20 weeks, in the second by neonatal subcutaneous injection of MSG. Fractions of inner mitochondrial membrane were separated using gradual ultracentrifugation.

Results: After HCD succinate-KoQ-oxidoreductase and H+-ATPase activity were lower by 1.2 (p < 0.05) and 1.8 times (p < 0.01) compared to the control group respectively. NADH-KoQ-oxidoreductase, KoQ-cytochrome c oxidoreductase, cytochrome oxidase activity increased by 1.3 (p < 0.05), 1.2 (p < 0.05) and 1.2 (p < 0.05) times respectively. In case of glutamate-induced steatosis NADH-KoQ-oxidoreductase activity, succinate-KoQ-oxidoreductase, KoQ-cytochrome c oxidoreductase, cytochrome oxidase activity, H+-ATPase activity decreased by 2.3 times (p < 0.01), 1.1 times (p < 0.05), 2.3 times (p < 0.01), 3.3 times (p < 0.001) and 3.3 times (p < 0.001) respectively.

Discussion/Conclusion: It was established that enzymatic activity of mitochondrial ETC complexes of rat hepatocytes is different under conditions of diet- and glutamate-induced steatosis development. We observed the decrease of ATP synthesis and the development of oxidative stress under modified diet. Also similar decrease of H+-ATPase activity simultaneously with the decrease of enzymatic activity of all ETC complexes under conditions of glutamate-induced steatosis, which indicates a dysfunction of liver mitochondria were observed.
Direct antiviral agent (DAA) treatment of chronic HCV infection results in rapid regression of transient elastography (FibroScan®) and validated fibrosis markers FIB4 and APRI

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Introduction: Novel direct antiviral agents (DAA) for chronic hepatitis C have revolutionized the HCV treatment. Rates of SVR have improved drastically since introduction of DAA in 2014. Transient elastography (TE) is the non-invasive technique to assess liver stiffness and TE values correlate with fibrosis stage. Indication for DAA treatment of HCV is often based on TE values. Histological regression of fibrosis has been well documented in long term studies. We here examined the changes in TE values and fibrosis scores within 18 months after successful DAA treatment of HCV.

Methods: 292 patients that received a DAA-based treatment for chronic HCV were included. TE values recorded prior to therapy (median 3 months, range 0–5 years) and within 18 months after HCV therapy were evaluated. Changes in TE values were correlated with FIB4 and APRI Scores as well as histological results where available.

Results: Median TE prior to DAA treatment was 15.45 kPa (IQR 10.15), median TE post treatment 9.3 kPa (IQR 10.4). This equals a TE regression of 35.64% within 18 months after successful HCV DAA treatment. Further subgroup analyses will be presented.
Liver enzymes correspondingly showed significant reduction, often already during DAA treatment. Average FIB4 and APRI prior to therapy were 3.66 and 1.88, respectively. Average post treatment FIB4 was 2.99 while post treatment APRI was 0.85. This results in a decrease in FIB 4 of 18.31% and a regression in APRI of 54.79%. Thus, both values fall below the published cutoff values for significant liver fibrosis following successful DAA treatment of chronic HCV.

Discussion/Conclusion: Patients with SVR after DAA therapy showed a rapid and significant regression of TE values within 18 months after end of treatment. Most patients displayed significant regression of liver stiffness within 3 months after end of treatment. Rapid decrease of TE is in concordance with regression of validated fibrosis scores FIB4 and APRI. It remains to be examined whether this indicates a true regression of fibrosis or merely resolution of chronic liver inflammation with subsequent improvement of laboratory parameters. Further investigation into TE values and correlating liver histology after DAA treatment is warranted.
Bone status assessed by quantitative ultrasound in children with inflammatory bowel disease: A comparison with DXA

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Objective: To determine the bone status in children with inflammatory bowel diseases (IBD) using quantitative ultrasound (QUS) measurement at hand phalanges and compare the obtained results with dual-energy X-ray absorptiometry (DXA).

Material and Methods: Fifty-one children (28 girls, 23 boys) with IBD, treated in the Public Clinical Hospital in Zabrze during the year 2013, were enrolled in the study. The average duration of IBD was 2.7 ± 1.7 years. 23 (47%) patients (with moderate/severe IBD) were treated with corticosteroids in the past and 4 (7%) children received steroids during the study. Nutritional status was assessed using Cole’s index. Bone mineral density (BMD) was measured with Hologic Explorer at the spine (s-BMD) and total body (TB-BMD). QUS was performed by means of DBM 1200 (IGEA, Italy). The control group for the QUS examination included 460 age-matched subjects (250 females and 210 males), selected from previously examined healthy children.

Results: Mean Ad-SoS Z-score did not differ significantly between patients with IBD and healthy controls (-0.19 ± 1.2 vs. -0.09 ± 1.04). There was also no difference in Ad-SoS Z-score between UC and CD subjects (-0.11 ± 1.12 vs. -0.25 ± 1.29). Ad-SoS correlated significantly with all DXA measurements (s-BMD: r = 0.69, p < 0.0015; TB-BMD: r = 0.74, p < 0.001: Although Ad-SoS Z-score correlated only with TB-BMD (r = 0.31, p < 0.02). s-BMD and TB-BMD Z-scores were lower than in the normal healthy population.

No significant differences were found in mineral density using DXA in UC and CD. Factors significantly correlated with BMD and Ad SoS were: Tanner stage and nutritional status. Duration of illness and steroids therapy did not affect bone status.

Conclusions: Low bone mineral density is an often complication of IBD in children. QUS is not an appropriate method for the assessment of bone status in pediatric patients with IBD. Nutritional status seems to have a greater impact on bone status than corticosteroids therapy.
Pulmonary manifestation of colitis ulcerosa in a 14-year-old girl

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Pulmonary manifestation of inflammatory bowel disease (IBD) are rare entity and has to be distinguished from infectious complications, side-effects of medications used in the treatment of IBD and pulmonary diseases associated with IBD. The incidence of symptomatic bronchopulmonary involvement in children seems to be much lower than in adults and the spectrum of lung pathologies is quite similar.

A 14-year-old girl with one year history of UC was admitted to the Clinical Hospital in Zabrze for chronic dry cough, sub-febrile state and loss of weight lasting over a month. She denied any significant dyspnea on exertion. She was treated in out-patients clinic for prior 2 months due to symptoms of upper respiratory syndrome disease. Her last flare of UC had been 6 month prior to the onset of the respiratory symptoms. She received mesalazine and azathioprine in therapeutic doses.

On admission to hospital routine bloods test revealed raised inflammatory markers and increased level of eosinophils. No infectious agents were detected, particularly we excluded tuberculosis. A chest radiograph showed unilateral foci of consolidation in right upper and middle lobe, without any improvement after antibiotic treatment. A CT scan was then performed which was reported focal consolidation in the peripheral parts of the upper and lower lobe (I, II, III, IV, VI, IX, X segments) of the right lung with accompanying lymphadenopathy on this side. Fiberoptic bronchoscopy was also performed and bronchial lavage samples were obtained from both lobes. This study did not show anything significant. The girl responded very good to systemic and inhaled steroids and after one month after steroid therapy chest X-ray showed improvement of the pulmonary infiltrates.

In conclusion, the manifestation in the lung vary and often represent a confounding diagnostic problem, especially in children. Steroids are effective in the majority of cases.
Therapeutic assessment and management in hepatic post-traumatic status associated with intricate pathology and complications

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Introduction: Post-traumatic hepatic injury may occur in patients with intricate pathology, such as cardiac dysrhythmia pathology, secondary to syncope episodes and in terms of anticoagulant drugs administration. Complex medical surveillance and an adapted therapeutic management requires extended monitoring when injuries are extensive, both for hemostasis and as well as for hepatic and cardiovascular protection.

Aim: To present therapeutic assessment difficulties in cases of intricate pathology and to estimate hepatic injury risks in patients with heart rhythm disorders.

Material and Methods: We present the case of an 83-year-old patient, underweight, with a history of cardiac rhythm disorders (extrasystolic ventricular arrhythmia, atrial fibrillation), oscillate arterial hypertension, osteoporosis, undergoing anticoagulant treatment, in appropriate dose for thrombosis prophylaxis, together with other therapies, for the associated pathology. She suddenly presented a short loss of consciousness, which caused her a collapse, in the same plane, followed by right thoracic-abdominal traumatism.

Results: Post-traumatic assessment revealed contusions and voluminous hepatic hematoma, rib fractures favored by osteoporosis, TA = 120/80 mmHg, high-frequency atrial fibrillation.
Imagistic, ultrasound and computed tomography highlighted the hepatic post-traumatic hematoma, allowing, alongside cardiac and biochemical explorations, proper monitoring. Initial therapy required hemostatics and antiarrhythmics. Anticoagulant medication was not recommended until hematoma consolidation.

Conclusions:
1. Liver contusion and hematoma may occur due to collapse within the same plane, in patients with risk factors such as: cardiac arrhythmia, hypertension, osteoporosis, anticoagulant, antiplatelet medication, circulatory insufficiency.
2. Conservative therapy, hemostatic in the first stage is useful, in order to control the degree of liver failure, aggregation factors, as well as heart disease.
3. Hepatic protection medication, rest, antiarrhythmic cardiac control, hypotensive drugs, without anticoagulants until hematoma becomes organized and prudence till its scarring can ensure a positive development.
Current challenges of biological therapy in non-alcoholic steatohepatitis associated with metabolic syndrome

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Introduction: Non-alcoholic steatohepatitis (NASH) is a frequent pathology and in some cases, may be associated with a metabolic syndrome, with clinical and biological perturbations, immediate and/or on long term. Classical therapy, especially statins and fibrates is often accompanied by adverse reactions and is non-tolerated at hepatic and muscular levels.

Aim: Presentation of new biological therapeutic possibilities for lipid imbalances correction, involving both the liver – steatohepatitis, as well as other affected structures within metabolic syndrome (vessels, heart, adipose tissue).

Patients and Methods: Non-alcoholic steatohepatitis, associated with metabolic syndrome was observed in a total of 30 patients. All patients were subjected to a 6-months treatment with statins; half of them associated also fibrates and pentoxifyllin in their therapeutic scheme.

Results: Statins tolerance, with proven efficacy through lipidogram and reduced steatosis degree was recorded in three quarters of the patients. In 7 patients (1/4) statins and/or fibrates treatment couldn’t be followed due to increased bilirubin level (cholestasis) and transaminases, above 5 times higher than normal; 1 patient also associated myopathy phenomena.

In these patients, to whom on one side, metabolic syndrome complications risks involve a long-term hypolipemiant therapy, and on the other side, liver damage due to steatohepatitis may worsen under classic treatment, there are current indications of biologic therapy (specific targeted molecules, such as PCSK9 inhibitors). Early experience with this type of therapy requires multiple aspects monitoring, concerning risks, effectiveness and long-term prognosis.

Conclusions:
1. Biological therapy targeting lipids disturbances is new, with complex action mechanisms and possibility of intervention in metabolic syndrome, for vascular and visceral complications prevention.
2. NASH may be aggravated during conventional hypolipemiant therapy, especially with statins, requiring current therapeutic intervention, such as the biologic one, in order to avoid side-reactions and complications.
3. Monitoring of new biologic therapies, with hypolipemiant effect opens new horizons and new research fields.
Ursodeoxycholic acid and therapeutic orientations in alcoholic liver disease associating bile acids and lipid perturbations

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Introduction: Alcoholic liver disease implies hepatobiliary and lipid metabolism modifications, imposing complex and targeted therapeutic implications.

Aim: To assess bile acids and cholesterol perturbations in patients with alcoholic liver disease, in order to establish targeted therapeutic orientations.

Patients and Methods: The study was conducted on a group of 110 patients, aged 25–65 years, diagnosed with alcoholic liver disease: alcoholic hepatitis (35 patients), hepatic steatosis (37 patients) and liver cirrhosis (38 patients).

Results: Intrahepatic cholestasis was present in 34 patients (31%). Cholesterol level variations (LDL and HDL) were recorded in 84 patients (76%). An increased level of cholesterol was observed in 62 patients (74%) from whom, 29 patients (47%) associated cholestasis by modifications of bile acids metabolism. A decreased cholesterol level was presented in 22 patients (26%), in 5 patients being associated with cholestasis (23%).

The treatment with ursodeoxycholic acid in association with dietary restrictions and treatment of hepatic disease and dyslipidemia, significantly improved the laboratory measurements regarding hepatocytes injury and cholestasis.

Conclusions:
1. The hepatobiliary axis plays a major role in maintenance the function of bile acids and cholesterol homeostasis.
2. In alcoholic hepatic disease there are important variations of cholesterol levels in association with bile acids modifications and cholestasis, requiring proper assessment and further monitoring.
3. The increase of cholesterol level in 76% of patients, the presence of cholestasis in 31% and the cholelithiasis in 16%, demonstrate the presence of bile acids and cholesterol perturbations in alcoholic liver disease, imposing special and adequate therapeutic management.
4. Ursodeoxycholic acid had a cytoprotective effect in cholestatic hepatocytes and improved the hepatobiliary disease, in associations with dietary measurements.
5. The treatment of the presented condition must be well established, well adapted, targeting 3 different axes: one for the hepatic disease itself, one for metabolism perturbations and one regarding dietary reasons.
Efficiency of molecular therapy with sorafenib in reperfusion of portal vein thrombosis due to hepatocellular carcinoma

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Introduction: Therapeutic possibilities in the presence of portal vein thrombosis are limited and challenging, given the severity of liver failure, portal hypertension or, in some cases, associated neoplasia.

Aim: Presentation of sorafenib molecular therapy efficacy, in portal vein thrombosis caused by associated hepatocellular carcinoma.

Patients and Methods: The study was conducted on 7 patients diagnosed with portal vein thrombosis and hepatocellular carcinoma, developed onto chronic liver disease background (cirrhosis), treated for 6 months with sorafenib, monitoring results regarding both portal thrombosis, as well as tumor status. The diagnosis was supported by investigations such as: ultrasound, Doppler, computed-tomography, angiography, associated with biological findings (coagulant balance, α1-fetoprotein) performed to patients with manifestation of portal and parenchymal decompensated cirrhosis. Patients were imagistic and biological monitored, monthly, during biologic therapy with sorafenib, in association with liver support medication (silymarin, arginine). Simultaneously, there were recorded hepatic tumor aspect and data regarding liver cirrhosis stage and etiology.

Results: All patients presented clinical and imagistic signs of portal vein thrombosis, with tumoral aspect, associating hepatic-spleen alterations, portal hypertension and ascites. Sorafenib molecular therapy, with protein kinase and VEGF (vascular-endothelial-growth-factors) inhibitory activity on tumoral growth, targeting portal thrombosis with tumoral aspect, was efficient, leading in 6 out of 7 cases to reperfusion of portal vein, intraportal thrombosis remission and portal hypertension reduction, in underlying territories. The contraindicated anticoagulants due to bleeding risk by hepatic failure and thrombocytopenia couldn’t be efficiently used in thrombosis, even without tumoral etiology. Improvement was also recorded in hepatic tumor: dimensions reduction, from a third and up to half of initial aspect. Liver cirrhosis severity manifestations were improved.

Conclusions:
1. Sorafenib molecular-targeted therapy was efficient in remission of portal vein thrombosis associated to hepatocellular carcinoma.
2. The 6-months’ treatment period, with monthly monitoring of portal venous thrombosis showed reperfusion and tumor downsize, under this revolutionary therapy.
New interferon-free therapy with targeted antivirals in chronic viral hepatitis C and possibilities of neuropsychiatric assessment

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**Introduction:** In viral C hepatic disease, chronic hepatitis and compensated cirrhosis, the use of new interferon-free therapies requires multidisciplinary assessment of possible side reactions.

**Aim:** Presentation of initial and post-therapeutic neuropsychiatric evaluation in patients with hepatitis C, in treatment with the combination: ombitasvir, paritaprevir, ritonavir +/- dasabuvir/ribavirin.

**Patients and Methods:** In the study were included 12 patients with chronic hepatitis C who met the conditions for interferon-free indication for 12 weeks. Before therapy initiation, besides clinical, imagistic and biological exploration needed for diagnosis, patients were subjected also to neuropsychiatric evaluation. For objectification of possible modifications, in the context of liver disease, cortical evoked potentials, visual type, have been performed and recorded (with prior ophthalmological examination).

**Results:** In all patients, neuropsychiatric clinical examination didn’t reveal abnormalities, but visual evoked potential recordings demonstrated perturbations existence in 5 patients. The changes consisted in prolonged latency periods, as amplitude and duration of the three constituent waves (N75, P100, N135). These disturbances, initially observed when initiating the therapy in 5 patients with chronic C hepatic disease may be influenced during interferon-free therapy, leading also to modifications to those patients with normal potential reactions. It is important to know whether the modified aspect was observed before initiation or during this type of therapy. The objective control, through visual stimulation reactions in patients with interferon-free therapy is required, in order to avoid any interfering with their daily, normal activities and to improve their quality of life.

**Conclusions:**
1. Therapeutic combination: ombitasvir, paritaprevir, ritonavir +/- dasabuvir/ribavirin in chronic viral C hepatitis, being a new antiviral targeted therapy requires control of potential intricate reactions, including neuropsychiatric manifestations.
2. At initiation and finalization of the new therapeutic scheme, antivirus C target, is important to evaluate and control neuropsychiatric status, in order to estimate multidisciplinary aspects with implications in patients’ activity.
Implications and therapy of drug-induced cholestatic liver disease in patients associating C and B hepatic viruses

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Introduction: Some drugs are important causes of liver damage which may have a cholestatic evolution needing therapeutically means.

Aim: To present hepatic cholestasis caused by anti-tuberculosis drugs, in order to achieve proper monitoring and further adequate therapeutic management.

Patients and Methods: The study was conducted on 30 patients, on a 6-years period; they were treated for long courses with anti-tuberculosis drugs and developed, in time, manifestations of hepatitis, in a cholestatic form. The performed investigations were biological (hepatic, immunological and tuberculosis tests), imagistic (ultrasound, computed tomography, x-ray, endoscopy) and pathological, by liver biopsy.

Results: All patients had in their history pulmonary or extra pulmonary tuberculosis (pulmonary [15] patients, genitourinary [6], pericarditis [2], peritonitis [3], bones tuberculosis [2], tuberculosis lymphadenitis [2]), for which they received anti-tuberculosis therapy, for 1 year period. The patients manifested after 1–5 years, a chronic hepatitis. Hepatic viral markers revealed the presence of C virus in 26 patients and B virus in 12. A cholestatic form of hepatitis occurred in 12 patients who associated virus infection, needing bile acid treatment and proper long term monitoring. Cholestasis decreased macrophage's activity and thus the re-activation of tuberculosis was observed in 2 patients.

Conclusions:
1. Prolonged treatment with anti-tuberculosis drugs associated sometimes with viral C, B aggression, induced chronic hepatitis and in 40% of cases, the occurrence was as cholestatic form.
2. The evolution was aggravated, on one side by liver damage caused by chronic hepatitis and hepatic drugs metabolism and on the other side, by the effect of liver disease on drugs metabolism.
3. Cholestasis reduced the function of macrophages and reactivated the tuberculosis, with difficult treatment issues.
4. Therapeutic management and new targets must be complex and very well adapted, in order to improve patients quality of life.
Burden of anaemia in upper GI bleeding in a secondary care hospital

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Objective: Upper gastrointestinal bleeding (UGIB) remains a considerable burden causing premature mortality throughout the world. Uncertainty exists about the best haemoglobin (Hb) measure to aim for acutely and on discharge in order to prevent premature mortality. However, the long term effects of anaemia post-UGIB has not been evaluated in secondary care cohorts, particularly to assess associations with mortality and the potential role of risk factors.

Methods: The secondary care patient sample was identified from University Hospital Birmingham informatics electronic patient records databases, which has a catchment population of more than 500,000. Demographics, clinical and follow-up information were collected on first admission per patients having: (i) upper gastrointestinal endoscopic procedure; (ii) a Hb measurement; and (iii) an admission between 1st January 2010 and 31st December 2014. Anaemia status was defined using the last Hb measurement before discharge according to high (Hb ≥ 10) or low (Hb < 10) as well as WHO anaemia status. UGIB and related conditions were detected using ICD10 codes: Gastric K25, Duodenal K26, Peptic K27, GI bleeding K92, Varices I85. One year survival post discharge was collected from UHB regional databases and was analysed using log rank statistics in Kaplan Meier survival curves. A naïve analysis of all data was compared against a matched analysis where patients were matched on propensity to anaemia using risk factors in a generalised logistic model.

Results: There were 1304 cases of UGIB identified in the 5 year period. The median range of patients was 67 years (interquartile range 54–80 years). 38.6% (504) of patients were female. Ethnicity included: Caucasian 81.7% (1065), South Asian 9.3% (121), and other 9.0% (118). Prevalence coding of past and current medical history was predominantly peptic ulcer (50.3%) but also included: liver disease (18.8%); diabetes mellitus (16.9%); cancer (16.6%); renal disease (15.5%); myocardial infarction (12.1%); and congestive cardiac failure (9.5%). Independent risk factors for overall mortality identified included: admission method (emergency or elective; p < 0.0001), age (p = 0.0005), gender (p < 0.001), body mass index (p < 0.001) and comorbidities (liver disease, renal disease, peptic ulcer all p < 0.001; heart failure and diabetes p < 0.02). One year survival between those discharged with a Hb ≥ 10 and < 10 when adjusted for age, gender, admission method, demographics, body mass index was 85.1% versus 76.7% (p = 0.0034). However, when comorbidities were also adjusted for, there was limited evidence to suggest overall mortality differences (p = 0.31).

Conclusions: This large-scale informatics study in a single-centre secondary care population has identified associations post-UGIB for a 1 year mortality difference dependent on Hb on discharge. However, this appears to be associated with comorbidities rather than anaemia per se. Further studies to assess the long-term effects of post-UGIB anaemia and the benefits of intervention are required.
Reference:

Bager et al., Aliment Pharmacol Ther. 2011

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The role for T cells in the pathogenesis of Crohn’s disease-associated fistulae

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Introduction: Fistulae represent a frequent complication in Crohn’s disease (CD) and surgical resection is often required. We have previously demonstrated that epithelial-to-mesenchymal transition (EMT) plays a critical role for fistula development. Tumor necrosis factor (TNF), interleukin (IL)-13, interferon gamma (IFNγ), IL-17A and IL-22 are highly expressed in transitional cells along fistula tracts in CD patients. Here, we analyzed the implication of the T cell-derived cytokines IFNγ, IL-17A and IL-22 in the event of EMT. Moreover, we investigated the composition of lymphocytes in the blood of CD patients suffering from fistulae compared to patients without fistulae or healthy controls.

Methods: Three-dimensional intestinal epithelial cell (IEC) constructs (spheroids) were stimulated with IFNγ, IL-17A and IL-22 to investigate the effects on EMT development. Further, CD4+ and CD25+ T cells were isolated from fistulizing CD patients’ blood or control blood samples and co-cultured together with IECs. Afterwards, mRNA expression levels of EMT-associated genes were analyzed.

Results: IFNγ induced the loss of the well-defined globular spheroid shape after day 7. However, mRNA levels for EMT-related transcription factors like SNAIL-1 were not up-regulated. IL-17A and IL-22 did not affect cell morphology. On a molecular level, both cytokines had no effect on the mRNA expression of EMT-associated genes, but prevented the TGF-beta (TGFβ)-induced up-regulation of e.g. SNAIL-1. The sorting of T cells isolated from blood of CD patients with fistulae revealed an elevated expression level of CD4+ and CD25+ T cells compared to healthy controls.

Discussion/Conclusion: Our data demonstrate that T cells may play a crucial role in the pathogenesis of CD-associated fistulae. IFNγ may be involved in the event of EMT in IECs however IL-17A and IL-22 are likely not implicated in EMT onset, and may prevent EMT-associated effects of TGFβ.
Allopurinol and azathioprine co-therapy or thiopurine dose splitting – Shifting the shunters in the mercaptopurine pathway in a paediatric IBD (pIBD) population: A single centre experience

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Background: The use of 6-thioguanine nucleotide (6-TGN) levels as a method to adjust thiopurine doses thus optimising therapeutic response whilst minimising toxicity, has dramatically improved patient's safety for drug-related side effects, however, they do still occur when patients shunt towards the MeMP pathway. Split dose thioguanine or allopurinol and low-dose thiopurine co-therapy are effective treatment options. Although data is available in adult IBD, there is paucity of data in pIBD. Split dose regimens and Co-therapy were introduced in our unit one year ago.

Aim: To evaluate the safety and therapeutic outcome of pIBD patients treated with either split dose azathioprine or azathioprine and allopurinol co-therapy for raised 6-TGN levels (> 450 units) and raised MeMP/6-TGN ratios (> 11).

Methods: We retrospectively reviewed our data since intervention started. Patients received daily 0.5 mg/kg (25%) of the standard azathioprine dose with 50 mg of allopurinol (if < 40 kg) and 100 mg (if > 40 kg), or a split dose (twice a day) of 2 mg/kg of azathioprine.

Results:
In the split dose group, 21 patients were identified (male n = 12, median age 11 years, age range 4–15 years), 10 patients were excluded for insufficient follow-up (< 6 weeks). For the 11 remaining patients, the median length of regime was 7 months (range 2–13 months). 8 had Crohn’s disease, 1 ulcerative colitis and 2 IBDU. Although in 9 (64%) patients 6-TGN/MeMP ratios normalised to < 11, in 10 (84%) patients the therapeutic 6-TGN levels where not reached, moreover, they actually decreased. Only 1 patient responded to the split dose regimen with normal 6-TGN levels plus normal ratio.

In the co-therapy group, 16 patients were identified (male n = 9, median age 10 years, age range 4–17 years), 5 were excluded due to insufficient follow-up and or switched to different therapy. The median length of co-therapy was 6 months, range 3–13 months). Out of the remaining 11 patients, 8 had Crohn’s disease, 1 ulcerative colitis and 2 IBDU. (9) 85% of pre co-therapy 6-TGN levels were sub-therapeutic, following co-therapy, 6 of these 9 (66%) moved into the therapeutic 6-TGN range, with normalisation in 90% of previously raised ratios.

Conclusions: Co-therapy treatment was superior to split dose regimens in our patient cohort, demonstrating that low-dose azathioprine and allopurinol co-therapy is a safe and effective treatment option in pIBD. This should encourage trialling Co-therapy before considering switching to other medication.
New anticoagulant therapy for portal vein thrombosis in patients with liver cirrhosis

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Introduction: Treatment of portal vein thrombosis (PVT) in patients with liver cirrhosis is not well established, and new drugs must be investigated. We intended to assess the safety and efficacy of sulodexidum to treat PVT in cirrhotic patients.

Methods: From June 2010 to March 2013, 810 patients with liver cirrhosis admitted to our clinic received Doppler ultrasound examination as a part of routine workup. 94 patients with non-neoplastic PVT and cirrhosis were prospectively enrolled (50 in the treatment group with sulodexidum 2 tb/day and 44 in the control group). In patients with gastro-esophageal varices, treatment was started after endoscopic eradication of varices by band ligation. In the treatment group, 16 patients (32%) had complete PVT and 34 patients (68%) had partial PVT. The mean MELD score was 14.6. Therapy was administered for a median period of 12 months and individuals were followed for a median time of 19 months.

Results: Complete recanalization of the portal vein occurred in 24% versus 0% of subjects, partial recanalization in 38% versus 27.2% of patients, and no response in 38% versus 72.8%. No significant side effects, particularly bleeding complications, were observed during therapy. The median value of platelets was 58,000/mm³ and 55,000/mm³ at the end of treatment. 4 of 28 patients who stopped treatment showed re-thrombosis of the portal vein at 1, 4 and 6 months. In univariate analysis, previous bleeding caused by portal hypertension and time between diagnosis and initiation of treatment < 14 days were positively associated with PV recanalization. Decompensation occurred during the study period significantly more in placebo than in sulodexidum-treated patients (placebo 18/44 [40.9%] vs. 11/50 [22%]; p = 0.01).

Discussion/Conclusion: Sulodexidum demonstrated to be safe and effective in the treatment of PVT in patients with liver cirrhosis and delayed liver decompensation.
TLR4 is still active in gp96-deficient macrophages

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Introduction: Gp96 is an endoplasmic reticulum chaperone for multiple protein substrates playing an important role in innate and adaptive immunity. Its absence in intestinal macrophages (iMACs) of Crohn’s disease patients is correlated with a loss of tolerance against the host gut flora. iMACS are crucial for pathogen recognition in the gastrointestinal tract. Our previous studies revealed a strong expression of TLR2 and 4 on inflammatory iMACS, in parallel with a specific loss of gp96. We aim to study the gp96’s role in TLR-function.

Methods: MM6 cells were stably transduced with lentiviral gp96-knockdown vector. Lentiviral vector particles were produced co-transfecting HEK293T cells. After transduction, cells were treated with LPS. In order to study the relevance in vivo, conditional LysMcre-gp96 knock-out (KO) mice were generated. Peritoneal macrophages were isolated from wild-type (WT) and KO mice, and treated with LPS. TLR2 and TLR4 expression was analyzed by flow cytometry and the expression of NFκB, IκB-α, IL-8, IL-6 and TNF-α was analyzed by Western blot, qPCR and ELISA. Results are expressed as percentage or fold induction ± SEM. All experiments were performed with an n ≥ 3.

Results: Flow cytometry experiments revealed non-significant differences between TLR4+ and TLR2+ gp96-shRNA compared with mock-transduced cells. The analysis of the expression of TLR4 and TLR2 receptors in peritoneal macrophages showed a similar slight decrease in KO compared with WT mice. TLR4 functionality was also analyzed and treatment with LPS induced a significant increase in the ratio pIkB-α/IκB-α in gp96-shRNA cells and in KO macrophages; and in pNFκB in both gp96-shRNA and in KO macrophages compared with non-treated mock-transduced and WT macrophages. LPS induced an increase in the expression of IL-8 in gp96-shRNA compared with mock-transduced. LPS also induced an increase in IL-8, IL-6 and TNF-α expression in KO macrophages.

Discussion/Conclusion: TLR4 receptor is still active and functional even in the absence of gp96 in macrophages.
Hypoxia positively regulates expression of the pH-sensing G-protein coupled receptor OGR1 (GPR68)

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Introduction: A novel family of proton-sensing G-protein coupled receptors (GPCRs), including ovarian cancer G-protein coupled receptor 1 (OGR1, also known as GPR68) has been identified to play an important role in pH homeostasis. Hypoxia is known to change tissue pH due to anaerobic glucose metabolism through the stabilization of hypoxia inducible factor (HIF)-1α. We investigated how hypoxia regulates the pH-sensing GPCR receptor OGR1 in the intestinal mucosa and associated cells.

Methods: OGR1 mRNA expression in murine tumors, human colonic tissue and myeloid cells was determined by RT-qPCR. The influence of hypoxia on OGR1 expression was studied in human MM6 cells, in primary human intestinal macrophages and in the intestinal mucosa of healthy volunteers and inflammatory bowel disease (IBD) patients. Changes in OGR1 expression in MM6 cells under hypoxia were determined upon stimulation with tumor necrosis factor (TNF), in the presence or absence of NF-κB inhibitors. In order to study the molecular mechanisms involved, chromatin immunoprecipitation (ChIP) analysis of the OGR1 promoter was performed.

Results: OGR1 expression was higher in tumor compared to normal murine colon tissue. Hypoxia positively regulated the expression of OGR1 in MM6 cells, primary human intestinal macrophages and in colonic tissue from inflammatory bowel disease (IBD) patients compared to healthy volunteers. In MM6 cells, hypoxia enhanced TNF-induced OGR1 expression was reversed by the inhibition of NF-κB. In addition to the effect of TNF and hypoxia, OGR1 expression was further increased at low pH. ChIP analysis revealed that HIF-1α, but not NF-κB, binds to this promoter region of OGR1 24 h after hypoxia in THP1 cells.

Discussion/Conclusion: The enhancement of TNF- and hypoxia-induced OGR1 expression under low pH points to a positive feed-forward regulation of OGR1 activity in acidic conditions, and supports a role for OGR1 in the pathogenesis of IBD.
Influence of a high-fat diet consumption on the development of cholelithiasis

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Background: It is known that some nutrients plays an important role in the development and treatment of cholelithiasis. The cholesterol is carried in micelles and vesicles by bile. Cholesterol crystals derived from thermodynamically unstable vesicles, during the first stage of gallstones formation. The aim of this research was to determine the effect of ingesting a high fat diet on blood lipids and bile, and its implication in the formation of gallstones.

Methods: 2 groups of Balb/c mice from the same litter were recruited: one control (n = 15), and the other (n = 15) treated with a high-fat diet (43% fat and 0.13% cholesterol). After 2 months, the animals were sacrificed, and blood and bile samples were obtained. We determined serum glucose and the corresponding lipid profiles. In bile samples, cholesterol and phospholipids levels were analyzed, and cholesterol transporters (vesicles and micelles) were separated by gel filtration chromatography.

Results: Treated animals showed: 1) increase by 49% in serum total cholesterol (control: 99 ± 10 mg/dl vs. treated: 148 ± 10 mg/dl; p < 0.05); 2) increase of 97% in HDL-cholesterol (control: 38 ± 11 mg/dl vs. treated: 75 ± 10 mg/dl; p < 0.05); 3) no change in LDL-cholesterol; 4) no variation in serum triglycerides; 5) no change in glycemia; 6) no change in biliary lipids (cholesterol: 4.4 ± 0.5 mM and phospholipids: 38.2 ± 0.9 mM); 7) increase of vesicular transporters in bile (control: 2.8 mM vs. treatment: 7.6 mM); 8) no variation in micellar transporter (control: 35.5 mM vs. treatment: 38.2 mM).

Conclusions: A high fat diet significantly increase total cholesterol and HDL-cholesterol, without changing LDL-cholesterol, triglycerides and glycemia. Even though we did not see changes in the total bile lipids, an increase in vesicular transporters of cholesterol in the treated group was observed. We conclude that a diet high in fat may contribute to the formation of gallstones in our experimental model.
Ultrasonography examination of the hand in inflammatory bowel disease

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Rheumatic manifestations are frequent in inflammatory bowel disease and are associated with a wide range of clinical patterns. There were defined new strategies for diagnosing and monitoring patients, with targeted treatment and tight control, which make necessary an accurate evaluation of the patients.

Introduction: The aim of this study was to evaluate the type and frequency of different structures involvement in the hand of patients with inflammatory bowel disease.

Methods: We designed an observational, transverse study, which included 108 consecutive patients diagnosed with inflammatory bowel disease, from 50 were diagnosed with Crohn’s disease and 58 with ulcerative colitis. All patients underwent clinical, biological and US examination, after informed consent was obtained. US examination was performed from the first to fifth metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, but included radiocubitocarpal (RCC) joint and flexor and extensor tendons too.

Results: A total of 220 hands were assessed, 100 in Crohn’s disease patients and 116 in ulcerative colitis. The mean ± SD for age was 50.91 ± 13.55 years in Crohn’s disease, 49.8 ± 10.73 years in ulcerative colitis. The global prevalence showed any US abnormalities at the hand level in 47 Crohn’s disease patients with respect to 17 patients in ulcerative colitis group. In all groups, the tendon involvement was present in less than 30% of the patients, the high global prevalence being explained by the joint involvement. In most of the patients with tendon involvement, we found joint involvement too. The most frequent US abnormality in Crohn’s disease patients was RCC synovitis (38/50) (76%), followed by MCP synovitis (23/50) (46%) and extensor tendons involvement (9/50).

Discussion/Conclusion: The results of the study show that in Crohn’s disease patients we find more joint involvement of the wrists and MCP joints.
The association between age and risk of cirrhosis, hepatocellular carcinoma or death in patients with chronic hepatitis C

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Patients with chronic hepatitis C may develop hepatic complication: cirrhosis and hepatocellular carcinoma, and also other non-hepatic comorbidities that negatively impact their likelihood of receiving or responding to antiviral treatment.

Introduction: This study aimed to determine the association between age subgroups and risk of cirrhosis, hepatocellular carcinoma or death in patients with chronic hepatitis C.

Methods: The study included 245 patients with positive hepatitis C virus. We analyzed the association between age subgroups (20–49, 50–64, 65–85 years) and risk of cirrhosis, hepatocellular carcinoma or death using Cox proportional hazards models. We also examined the effect of treatment with a sustained viral response on these outcomes in each age subgroup.

Results: The age distribution was 36.8% 20–49 years old, 57.6% 50–64 years old and 5.6% 65–85 years old. Risk of cirrhosis, hepatocellular carcinoma and death was significantly elevated in elderly patients (HR cirrhosis = 1.14 [1.00–1.29], HR hepatocellular carcinoma = 2.44 [1.99–2.99], HR death = 2.09 [1.98–2.22]) compared with younger patients. The incidence of hepatocellular carcinoma was 8.4 per 1000 PY in the elderly compared with 2.6 per 1000 PY and 5.7 per 1000 PY, among the 20–40 and 50–64 age groups, respectively. Elderly patients were significantly less likely to receive antiviral treatment (3.8% vs. 14.8% and 19.1%, p < 0.0001), but among those who receive treatment sustained viral response was associated with a reduction in risk of developing cirrhosis (HR = 0.34; 0.18–0.66) and hepatocellular carcinoma (HR = 0.60; 0.22–1.61) and all-cause mortality risk (HR = 0.52; 0.33–0.82).

Discussion/Conclusion: Elderly patients with chronic hepatitis C are more likely to develop hepatocellular carcinoma than younger patients but have traditionally received less antiviral treatment than younger patients. However, receipt of curative treatment is associated with a benefit in reducing cirrhosis, hepatocellular carcinoma and overall mortality, irrespective of age.
Microvascular density analyzed with endothelial cell markers in colorectal cancer associated with Crohn’s disease

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Angiogenesis is an important step in the process of cancer growth. It promotes metastatic spread by providing the means for cells to detach from the primary tumor and to travel in the bloodstream to distant metastatic sites.

Introduction: The purpose of this study was to determine the neoangiogenesis in colorectal cancer associated with Crohn’s disease with endothelial cell markers CD31, and CD105, and tried to observe the differences between these antibodies.

Methods: The study included a group of patients diagnosed with colorectal cancer and Crohn’s disease. Immunohistochemical study was conducted on a group of 48 patients included in the histopathological study. Were used samples resulting from endoscopic biopsies from which was taken a fragment of tumor tissue either by colonoscopy with biopsy. For immunolocation of blood vessels, fixed paraffin tissue sections were subjected to immunostaining for CD 34, CD31 and CD105.

Results: The average values of CD34 for moderately differentiated cases are lower than for well-differentiated cases, which is somewhat unexpected, and lower than the poorly differentiated, none of the differences were however statistically significant. Looking at the overall results, we found levels of CD34 to be almost double, compared to CD31 or CD105, average values for CD31 are significantly higher than CD105 values. The CD 31 antibody increases in parallel with the CD 105 antibody for cases examined in this study. Mean value for CD105 are statistically significant in terms of grading, which demonstrates that CD 105 antibody is a valuable tool for assessing grading for colorectal cancer.

Discussion/Conclusion: Giving the fact that the mean percentage of the MVD marked by CD105 and CD31 are relatively close to each other, and the fact that in the maturation process of neoformation vessels expression of CD105 can be found simultaneously with the expression of CD31, we can conclude that an important number of vessels (around 40%) that can be found in tumor area are neoformation vessels, being an important assessment for the choice of the correct and effective treatment in colorectal adenocarcinoma.
Asymmetric dimethylarginine levels and the severity of liver disease

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Introduction: Asymmetric dimethylarginine (ADMA) plays an important role in pathogenesis of endothelial dysfunction, whereas increased ADMA levels are related to increased cardiovascular risk. Previous studies suggest that hepatocellular damage may be the main determinant of elevated ADMA levels in a liver disease. The aim of this study was to determine the alterations of ADMA levels based on the severity of the liver disease.

Methods: Sixty-eight patients (56 male), with histologically or clinically proven cirrhosis were included in the study. ADMA levels were determined using validated competitive enzyme-immunoassays procedure. The subjects were divided into three subgroups (A: n = 9; B: n = 33; C: n = 26) based on the degree of the liver involvement, as assessed by the Child-Pugh’s score (CPS). Patients were stratified according to pre-existing cardiovascular and renal risks. The data were tested using non-parametric Kruskal-Wallis test, followed by post-hoc analysis.

Results: There was a statistically significant difference in ADMA levels between CP groups ($\chi^2 = 12.774$, $p = 0.002$). Post-hoc analysis revealed that ADMA levels were significantly higher in Child Pugh class C versus class A ($\chi^2 = 4.716$, $p = 0.030$) and Child-Pugh class C versus class B ($\chi^2 = 11.606$, $p = 0.001$).

Discussion/Conclusion: Our data demonstrate that Child Pugh C patients have higher ADMA levels than those with milder stages of the disease. Advanced liver damage impairs its normal metabolism and leads to accumulation of ADMA, which subsequently given its vascular effects, may determine elevated vascular resistance and the progression of liver disease. Further studies are needed to provide insight into this novel mechanisms of liver disease with the aim to identify potential therapeutic opportunities.
Viekirax and Exviera treatment is associated with significant improvement of FIB4 and APRI scores in cirrhotic patients

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Introduction: Chronic hepatitis C (CHC) is still a significant clinical problem in healthcare. Non-invasive serum fibrosis markers: APRI and FIB4 were accepted for estimation of fibrosis in CHC.

Methods: 37 CHC patients (18 males, 19 females) were enrolled to the Viekirax plus Exviera therapy accordingly to Polish National Health Service recommendations in Outpatients Clinic, Pomeranian Centre for Infectious Diseases and Tuberculosis in November and December 2015. The change of FIB4 and APRI score between baseline and week 12 therapy in cirrhotic (24/37) and non-cirrhotic (13/37) subjects was analyzed.

Results: Cirrhotic patients have significantly higher bilirubin concentration, lower hemoglobin concentration; PLT and WBC counts. Genotype 1b was detected in 36/37, genotype 4 in 1/37 cases. Baseline FIB4 and APRI scores had significant correlation with liver stiffness (R = 0.71; R = 0.75), moderate with clinical manifestation of liver cirrhosis (R = 0.47; R = 0.40), accordingly. In one case therapy was stopped after week 8 because of sepsis. A viral load was undetectable in all 37 finished therapy patients. We observed higher reduction of mean APRI and FIB4 score in cirrhotic (2.87 ± 2.37 to 0.55 ± 0.16; and 6.96 ± 4.71 to 3.94 ± 2.06, respectively) than non-cirrhotic patients (0.33 ± 0.02 to 0.21 ± 0.05; and 1.13 ± 0.13 to 1.00 ± 0.4, respectively). Bilirubin increased in all treated patients but significantly (p = 0.0082) only in cirrhotic patients (week 4).

Discussion/Conclusion: Successful antiviral therapy with Viekirax and Exviera associates with significant reduction of APRI and FIB4 score in cirrhotic and non-cirrhotic CHC patients.
Significant improvement of APRI and FIB4 scores in chronic hepatitis C patients successfully treated with PEG-interferon α with ribavirin

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3Department of Tropical Medicine & Epidemiology, ul. Powstania Styczniowego 9b, 81-519, Gdynia, Poland

Introduction: Chronic hepatitis C (CHC) is still a significant clinical problem in Polish healthcare system. Non-invasive serum fibrosis markers: APRI and FIB4 were accepted for the estimation of fibrosis in CHC.

Methods: We retrospectively analyzed 65 consecutive CHC patients (36 males, 29 females), enrolled to the PEG-interferon α with ribavirin therapy accordingly to EASL recommendations in Outpatients Clinic, Pomeranian Centre for Infectious Diseases and Tuberculosis between 2006–2012. To the study we enrolled only these patients (selected out of about 1200), who had necessary data to calculate APRI and FIB4 scores.

Results: The change of FIB4 and APRI score between baseline and week 24 after therapy was analyzed in patients’ groups accordingly to the therapy effect. Baseline minotransferases activity, blood morphology (except PLT count), viral load and demographic data were similar in studied groups. We determined HCV genotype in 61/65 patients: genotype 1 in 43/65, genotype 3 in 16/65 and genotype 4 in 2/65 case. Baseline FIB4 and APRI scores had significant correlation with liver histology (R = 0.68; R = 0.57), respectively. Viral load was undetectable in 70% of patients at the end of antiviral treatment (end of treatment, EOT), but sustained viral response (SVR) was achieved only in 33% of cases. We observed significantly higher reduction of mean APRI and FIB4 score in patient with EOT viral response (1.10 ± 0.17 to 0.68 ± 0.19; and 2.01 ± 0.25 to 1.76 ± 0.24, respectively) than non-responders (1.41 ± 0.23 to 1.25 ± 0.24; and 2.60 ± 0.37 to 2.83 ± 0.41, respectively). A significant reduction of APRI score was observed after antiviral therapy in all treated subjects (p = 0.00005), but not FIB4 score (p = 0.59).

Discussion/Conclusion: Successful therapy with PEG-interferon α plus ribavirin improved APRI and FIB4 scores in CHC patients. Moreover, APRI score significantly decreased in all PEG-interferon α with ribavirin therapy CHC patients.
Mesenchymal stem cells are emerging curative option in hepatic fibrosis model of rats

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2Marmara University, Medical Faculty, Department of General Surgery, İstanbul, Turkey
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Liver’s regenerative capacity is interrupted with hepatic fibrosis. Cellular therapy is a promising approach that may preclude the need for OLT. Among them, mesenchymal stem cells (MSCs) have potential to Trans-differentiate into hepatic cells.

Aim: To show the effects of bone marrow MSCs transferred via the tail vein to the rats having hepatic fibrosis produced by common bile duct ligation (CBDL) model.

Method: Rats were divided into three groups; 1) CBDL rats that were given MSCs (CBDL+MSC), 2) CBDL rats given phosphate-buffered saline (PBS) (CBDL+PBS), 3) Healthy rats that were sham operated and given MSCs (Healthy+MSC). We analyzed the in vivo functional effects by glucose production, albumin secretion and serum ALT levels. MSCs were labeled with GFP to check the localization of stem cells and to get idea for the regenerative capacity in the injured liver. Splenocytes were isolated from spleen and cultured with Anti-CD3 and Anti-CD28. Immunologic parameters were analyzed with flow cytometry.

Results: Histologically, liver fibrosis developed in CBDL rats while the healthy rats group did not show any alteration in liver architecture. Bilirubin levels were as follows: Group 1: 0.15 (0.11–0.14), Group 2: 6.80 (5.97–8.01), Group 3: 6.77 (5.95–7.44) mg/dl. MSCs significantly suppressed the rats’ splenocyte proliferation more in CBDL+MSC compared with CBDL+PBS group. NK cells in peripheral blood significantly increased more in CBDL+MSC compared with CBDL+PBS. Peripheral CD4+CD25+ ratio increased in CBDL+PBS compared with CBDL+MSC. MSCs significantly suppressed the TNF-α and IL-1β pro-inflammatory levels in CBDL+MSC compared with CBDL+PBS.

Discussion: Our findings suggest bone marrow derived MSC injection treatment may appear promising in liver injury and future clinical therapies are warranted.

Keywords: Hepatic regenerative medicine, cellular therapy, bone marrow-derived stem cells, common bile duct-ligated cirrhotic model, rats
Mycophenolate mofetil and tacrolimus as second-line therapy in autoimmune hepatitis: An international multicentre study

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**Background:** Corticosteroids alone or in combination with azathioprine are the standard treatment of autoimmune hepatitis (AIH). This therapy is not tolerated or insufficient to control disease activity in up to 20% of patients. We aimed to study the efficacy of mycophenolate mofetil (MMF) and tacrolimus as second-line therapy in AIH patients who were resistant or intolerant to standard therapy.

**Patients and Methods:** In this retrospective study, we evaluated data from 2260 patients with AIH and overlap syndromes (figure 1). Patients on second-line therapy were categorized according to response to standard therapy: Group I were complete responders, Group II were partial responders and Group III non-responders.
Results: A total of 254 patients (154 MMF, 100 tacrolimus) with a median follow up of 54 (1–190 months) were included in the study. MMF and tacrolimus induced or maintained biochemical response in 88.2% and 95.2%, respectively, of Group I patients ($p = 0.344$). In difficult-to-treat patients (Group II–III), non-response was significantly more common for MMF than for tacrolimus (44.3% vs. 19.0%, $p = 0.003$), and complete response was significantly more common for tacrolimus than for MMF (56.9% vs. 32.8%, $p = 0.008$, respectively; table 1). The rates of liver-related deaths or liver transplantation were similar in the MMF and tacrolimus groups (13.7% vs. 11.1%, log-rank $p = 0.522$; figure 2). Eleven MMF (7%) and 12 tacrolimus (12%) patients developed side effects that required therapy withdrawal.

Conclusions: Long-term therapy with MMF and tacrolimus is generally well tolerated in AIH. Both agents are equally effective in responders to conventional therapy, but tacrolimus seems superior to MMF in patients with incomplete response or non-response to standard therapy.

Keywords: autoimmune hepatitis, mycophenolate mofetil, tacrolimus, second-line therapy, overlap syndrome.

Table 1: Efficacy of MMF and tacrolimus in patients with autoimmune hepatitis

<table>
<thead>
<tr>
<th></th>
<th>MMF (n = 154), %</th>
<th>Tacrolimus (n = 100), %</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of response</td>
<td>38 (24.7)</td>
<td>13 (13.0)</td>
<td>0.023</td>
</tr>
<tr>
<td>Response Complete/Partial</td>
<td>116 (75.3)</td>
<td>87 (87.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>102 (66.2)/14 (9.1)</td>
<td>73 (73.0)/14 (14.0)</td>
<td>0.255/0.222</td>
</tr>
<tr>
<td><strong>Group I (n = 135)</strong></td>
<td><strong>n = 93</strong></td>
<td><strong>n = 42</strong></td>
<td></td>
</tr>
<tr>
<td>Lack of response</td>
<td>11 (11.8)</td>
<td>2 (4.8)</td>
<td>0.344</td>
</tr>
<tr>
<td>Response Complete/Partial</td>
<td>82 (88.2)</td>
<td>40 (95.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>82 (88.2)/—</td>
<td>40 (95.2)/—</td>
<td></td>
</tr>
<tr>
<td><strong>Group II (n = 60)</strong></td>
<td><strong>n = 34</strong></td>
<td><strong>n = 26</strong></td>
<td></td>
</tr>
<tr>
<td>Lack of response</td>
<td>8 (23.5)</td>
<td>2 (7.7)</td>
<td>0.163</td>
</tr>
<tr>
<td>Response Complete/Partial</td>
<td>26 (76.5)</td>
<td>24 (92.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (50)/9 (26.5)</td>
<td>18 (69.2)/6(23.1)</td>
<td>0.134/0.764</td>
</tr>
<tr>
<td><strong>Group III (n = 59)</strong></td>
<td><strong>n = 27</strong></td>
<td><strong>n = 32</strong></td>
<td></td>
</tr>
<tr>
<td>Lack of response</td>
<td>19 (70.4)</td>
<td>9 (28.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Response Complete/Partial</td>
<td>8 (29.6)</td>
<td>23 (71.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (11.1)/5 (18.5)</td>
<td>15 (46.9)/8(25.0)</td>
<td>0.003/0.550</td>
</tr>
<tr>
<td><strong>Group II–III (n = 119)</strong></td>
<td><strong>n = 61</strong></td>
<td><strong>n = 58</strong></td>
<td></td>
</tr>
<tr>
<td>Lack of response</td>
<td>27 (44.3)</td>
<td>11 (19.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Response Complete/Partial</td>
<td>47 (81.0)</td>
<td>33 (56.9)/14 (24.1)</td>
<td>0.008/0.879</td>
</tr>
</tbody>
</table>

Group I: patients with complete response to standard therapy; Group II: patients with partial response to standard therapy; Group III: patients with no response to standard therapy.
Figure 1: Study flow chart for patient inclusion

AIH patients  
n= 2260

Excluded:  
Standard therapy n= 1951

2nd line therapy  
n= 309

Excluded:  
Cyclosporine n=18, Everolimus n=2, Methotrexate 
n=1, cyclophosphamide n=1, rituximab n=1

Excluded:  
Insufficient data or non-compliance to therapy  
MMF n=18, tacrolimus n=14

Study group  
MMF n= 154  
Tacrolimus n= 100

Figure 2: Cumulative survival from liver-related death and transplantation in patients treated with MMF and tacrolimus (p = 0.522).
Conflict of interest: None

Financial support: No source of support in the form of grants, equipment or drugs.

Authors’ contributions: CE, SW, EMY and EO conceptualized the study. CE, HY, HH, SW and TP collected and analysed data, wrote the manuscript. MC and SH analysed data and performed statistical analysis. RAB, NFM, QW, LM, MW, SV, MT, FSL, HUM, PM, FG, DK, AP, AHB, TDS, MC, XM, AJML, TB and EO contributed data and approved final manuscript. EMY, MH, EO and SW interpreted data and prepared manuscript for the final submission.
Can polyphenol compounds be recognized as novel therapeutic targets in NAFLD?

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²Bogomolets National Medical University, Kyiv, Ukraine

Introduction: Polyphenols characterized by the presence of large multiples of phenol structural units. They are naturally abundant in the plants providing the protection against ionizing radiation, against microbial infections and participating in cell molecular signaling processes. One of the main polyphenolic substance in human body is melanin which characterized by strong antioxidant properties and can attenuate inflammation caused by excessive sunbathing.

We have paid attention to melanin produced by yeast Nadsoniella nigra strain X-1 as novel antioxidant and anti-inflammatory agents with low toxicity. In current study we aimed to investigate the preventive effect of melanin on the monosodium glutamate (MSG) induced NAFLD model in rats.

Methods: The study was carried out on 45 Wistar rats that were divided into 3 groups: intact, MSG- and MSG+ melanin groups (n = 15 in each group). Newborn rats of MSG- and MSG+ melanin groups were administered with MSG (4 mg/g, 8 µl/g, subcutaneously). Since the age of 1 month, rats of MSG- group were treated with water (0.25 ml/100 g), rats of MSG+ melanin groups – with melanin (1 mg/kg) dissolved in water (0.25 ml/100 g). Introduction had been performed intermittently (two-week courses alternated with two-week breaks) for 3 months. To assess morphological changes in liver we used NAS (NAFLD activity score).

Results: We found significantly lower total score (1.0 ± 0.19 vs. 3.33 ± 0.36, p < 0.001), degree of steatosis (0.73 ± 0.18 vs. 1.80 ± 0.17, p < 0.001) and manifestation of lobular inflammation (0.27 ± 0.11 vs. 1.20 ± 0.17, p < 0.001) due to NAFLD activity score in MSG+ melanin group compared to MSG- obesity. Melanin reduced the content of IL-1β in rat serum and restored the level of anti-inflammatory cytokines (IL-10, TGF-β) to the control values.

Discussion/Conclusion: Thus, the administration of melanin can prevent development of NAFLD/NASH in rats with MSG-induced obesity and can be considered as possible novel therapeutic agents but further studies to confirm its action needed.
Proteomic analysis of serum from patients with irritable bowel syndrome

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Introduction: Irritable bowel syndrome (IBS) is one of the most common functional disorders of the gastrointestinal tract. It is characterized by the presence of a different symptoms and signs in adult or children that include cramping, abdominal pain, increased gas, altered bowel habits, food intolerance, and bloating. The exact cause of irritable bowel syndrome (IBS) is unknown. In the present study, proteomics technology was used to monitor differences in protein expression among adult patients with IBS.

Methods: Male and female serum samples from 36 adults with IBS and 12 healthy individuals were subjected to 2-dimensional gel electrophoresis. Following the relative quantitation of protein spots exhibiting a differential expression between the 2 groups by densitometry, the spots were further characterized by matrix-assisted laser desorption tandem time-of-flight mass spectrometer.

Results: From comparisons of quantitative spectral counting data among the IBS group and controls, a total of 145 proteins were identified. Table 1 illustrates the proteins showing distinctive changes (increased expression) in IBS group vs controls. Most of them are involved in homeostasis of intestinal function, intestinal tract immunity and inflammation.

Conclusion: Further analyses and protein identification of the differential protein peaks will aid in accurately understanding of IBS etiopathophysiology.
Table 1: Proteins with increased expression in IBS group versus controls

<table>
<thead>
<tr>
<th>Protein name</th>
<th>Protein symbol</th>
<th>MW</th>
<th>pI</th>
<th>Mascot score</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotransferrin</td>
<td>TFRC</td>
<td>79234.00</td>
<td>7.00</td>
<td>325</td>
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<tr>
<td>Complement factor B</td>
<td>C5AB</td>
<td>66497.00</td>
<td>6.70</td>
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<td>Alpha-1B-glycoprotein</td>
<td>A1BG</td>
<td>54790.00</td>
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<td>Complement C3</td>
<td>CO3</td>
<td>189569.00</td>
<td>6.00</td>
<td>37</td>
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<td>Retinol-binding protein 4</td>
<td>RET4</td>
<td>23337.00</td>
<td>5.70</td>
<td>71</td>
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<tr>
<td>Ig gamma-1 chain C region</td>
<td>IGHG1</td>
<td>38665.00</td>
<td>9.40</td>
<td>69</td>
<td>28</td>
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<tr>
<td>Sere/threonine-protein phosphatase 2A regulatory subunit B</td>
<td>P2RK3C</td>
<td>53567</td>
<td>4.93</td>
<td>42</td>
<td>11</td>
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<tr>
<td>Testis-expressed sequence 43 protein</td>
<td>TEX43</td>
<td>15670</td>
<td>10.13</td>
<td>41</td>
<td>43</td>
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<tr>
<td>Zinc finger protein 623</td>
<td>ZN623</td>
<td>63064</td>
<td>9.70</td>
<td>40</td>
<td>7</td>
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<td>Receptor-type tyrosine-protein phosphatase C</td>
<td>PTPRC</td>
<td>14868.44</td>
<td>5.74</td>
<td>40</td>
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<tr>
<td>Actin-related protein 6</td>
<td>ARP6</td>
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<td>Tufelin-interacting protein 11</td>
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<tr>
<td>Coiled-coil domain-containing protein 27</td>
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<td>75821</td>
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<td>Ankyrin repeat domain-containing protein 20B</td>
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<tr>
<td>Zinc finger protein 138</td>
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<td>37</td>
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<td>Ectoderm-neural cortex protein 1</td>
<td>ENC1</td>
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<td>102329</td>
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<tr>
<td>Glial fibrillary acidic protein</td>
<td>GFAP</td>
<td>49977</td>
<td>5.30</td>
<td>36</td>
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<tr>
<td>Schlafen family member 5</td>
<td>SLF5N</td>
<td>102590</td>
<td>9.44</td>
<td>33</td>
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</tr>
</tbody>
</table>
Obesity as independent risk factor for hepatocellular carcinoma development in patients with HCV infection and chronic alcohol consumption

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

Methods: We studied 88 patients with chronic HCV infection: 59 heavy alcohol drinker patients (intake over 80 g ethanol/day for more than 10 years) and 29 non-alcoholic patients. The alcoholic patients were divided in two groups: obese alcoholic patients (A group, 37 cases, BMI > 32 kg/m²) and normoponderal patients (B group, 22 cases). The C group contained 29 non-alcoholic patients in the last 5 years, but 9 patients had history of low alcohol consumption. We monitored the clinical manifestations, alcohol consumption, BMI, AFP level, liver function tests and histological aspects after 12, 24 and 36 months.

Results: At baseline, the mean value of alcohol consumption was: 116.25 g/day in the A group and 124.72 g/day in the B group. After 6 and 12 months, the mean value of AST/ALT ratio was < 1 in the A and B groups and between 1 and 1.3 in C group. This level of AST/ALT ratio was maintained for whole period and wasn't observed a significant difference between normoponderal and obese patients. Sub-unitary AST/ALT ratio was correlated with the presence of histological active hepatitis and exclusively with the presence of the C virus infection. After 12 months, steatosis was most frequent in the A group (89.19%), comparative with B group (68.19%) and C group (55.18%). 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 increased in patients who associated obesity with alcohol consumption: 37.83% in the A group, 27.28% in the B group and 17.25% in C group. HCC was developed in 9 cases (10.22%): 5 cases in the A group, 3 cases in B group and only 1 case in C group. The association between presence of C virus and alcohol abuse, in patients which developed HCC, was correlated with tumor dimensions, BMI, but no correlation with AFP.

Discussion/Conclusion: Association of the HCV infection with alcohol abuse was correlated with the high steatosis grade and severe fibrosis. The risk of development of HCC was higher in obese patients with chronic alcohol consumption and long history of C virus infection.
The lifestyle changes and the probiotics in association with usual therapies in the treatment of the non-alcoholic steatohepatitis in obese patients

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Introduction: We assessed the effectiveness of association between improved lifestyles and combined therapy with ursodeoxycholic acid (UDCA) and probiotics in the treatment of non-alcoholic steatohepatitis (NASH). The efficacy of probiotic therapy in modifying liver function and her effects on hepatic steatosis or steatofibrosis were also evaluated.

Methods: We studied 53 patients with NASH and obesity. Group A was composed of 18 cases which received UDCA (15–28 mg/kg/day) and probiotics: Lepicol (L. plantarum, L. delbrueckii, L. acidophilus, L. rhamnosus and B. bifidum) or eubiotic (L. rhamnosus, Bifidobacterium). The B group contain 24 cases, treated with UDCA and vitamin E (400 IU twice a day). The C group consist of 11 cases, treated with pentoxifylline (1200 mg/day for 3 months). All patients have been recommended lifestyle changes, but lifestyle improvement was monitored only in the A and C groups. We evaluated the liver function tests, serum lipids and BMI after 2, 6 and 12 months. The biopsy of the liver was performed before and after therapy.

Results: Serum aminotransferases had high level in 46 patients and the lipid profile was: hypercholesterolemia (19 cases), hypertriglyceridemia (10 cases) and 11 cases with both. In group A, mean value of serum ALT decreased from 89.19 ± 22.7 U/l to 52.12 ± 16.8 U/l after 2 months. Serum ALT was moderately reduced (with 19.3 ± 7.2 U/l) after 2 months in B group and C group (22.1 ± 6.8 U/l). In the A group the mean values of total cholesterol, HDL and TNF-alpha were more decreased comparative with B group and C group. After 4 months the normalization rates of ALT was 88.89% in A group, 73.33% in B group and 81.82% in C group. Histopathologic examination indicated improvement the steatosis grade: 83.34% in A group, 70.84% in B group and 45.46% in C group. Also, the fibrosis score was more reduced in the A group. We could not establish a correlation between the values of serum aminotransferases and other parameters, but the BMI > 32 kg/m² and high values of serum ALT were associated with the steatosis grade. Patients which associated UDCA therapy with probiotics and low caloric diet, had a better and quickly response.

Discussion/Conclusion: The combined therapy with UDCA and probiotics, sustained by lifestyle modification, significantly improves aminotransferase levels, HDL and steatosis grade. The modulation of the gut microbiota in association with low caloric diet can assure a significantly improvement of the efficacy of usual therapies in patients with NASH and obesity.
Prevalence and antibiotic treatment of small intestinal bacterial overgrowth in patients with Crohn’s disease

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Introduction: Small intestinal bacterial overgrowth (SIBO) sometimes deteriorates the clinical course of Crohn’s disease (CD) but its treatment is not clearly defined. Our aim was to evaluate the prevalence of SIBO in patients with CD and to assess the efficacy and compliance of ciprofloxacin and metronidazole treatment in cases with SIBO by using a lactulose hydrogen breath test (LHBT).

Patients and Methods: 36 adult unselected patients (17 females, 19 males; mean age 32.7 years) with CD and 10 healthy subjects (4 females, 6 males; mean age 34.5 years) consented to participate in the study. Eight of the patients had undergone an ileocolic resection, the rest were non-operated. After an oral dose of 10 g lactulose, breath hydrogen concentrations were recorded every 15 min for 120 min. Patients with positive LHBT were treated with ciprofloxacin (200 mg b.i.d.) and metronidazole (500 mg t.i.d.) for 10 days and the test was performed repeatedly. Compliance and side-effect incidence were also evaluated.

Results: In comparison to controls, CD patients had significantly \( p < 0.05 \) higher basal breathed hydrogen (14.64 ± 1.07 ppm; range: 3–51 vs. 5.56 ± 0.96 ppm; range: 2–12). Out of 36 CD patients, SIBO was documented in 9 (25.0%) but in none of the controls \( p < 0.05 \). The prevalence of SIBO was significantly higher in patients with previous surgery 5/8 (62.50%) than in non-operated patients 4/26 (15.38%). The mean basal breathed hydrogen in CD patients with evidence of SIBO (37.11 ± 2.86 ppm) was significantly reduced (10.67 ± 1.58 ppm) after antibiotic treatment. SIBO eradication was achieved in all but one (88.9%) of the patients. No adverse effects were observed.

Conclusions: SIBO is a frequent condition in CD especially in the case of previous ileocolic surgery. Short-term administration of ciprofloxacin and metronidazole was well-tolerated and effective treatment for these patients. The LBHT is a simple, noninvasive, inexpensive and repeatable method for diagnosis and monitoring of SIBO in CD patients.
Prevalence of autoimmune diseases associated with coeliac disease

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Introduction: Coeliac disease (CD) is a chronic inflammatory autoimmune enteropathy. It is frequently associated with autoimmune disorders. The aim of this study was to evaluate the prevalence of autoimmune diseases during CD and their evolutionary features under gluten-free diet.

Methods: We investigated all the CD patients admitted in our department in the period between January 1996 and December 2015. We analysed their medical records in order to determine the AD associated to CD in every patient.

Results: A total of 78 patients were studied. 14 patients had an associated autoimmune disease (17.94%). Their mean age was 37 years with a female predominance (sex ratio = 0.27). The autoimmune disease was diagnosed before the CD in 6 patients (42.85%), at the same time as CD in 4 cases (28.57%) and after in 4 patients (28.57%). Nine patients had only one autoimmune disorder, and 5 had two. These autoimmune diseases were mainly represented by type 1 diabetes in 60% of cases and hypothyroidism in 20%. Other autoimmune diseases were recorded in some patients: autoimmune hepatitis (n = 2), Sjögren’s syndrome (n = 1), primary biliary cirrhosis (n = 1), pernicious anaemia (n = 1), systemic Lupus erythematosus (n = 1), and vitiligo (n = 1). Each patient undertook a gluten-free diet in addition to a specific treatment of the diagnosed autoimmune disease. We compared the evolution of CD between patients having or not an associated autoimmune disease. There was no significant correlation between autoimmune disorders and lack of response to gluten-free diet in CD (p = 0.27).

Conclusion: CD is often associated with various autoimmune diseases. These disorders should be systematically sought in order to avoid any diagnostic and therapeutic delay.
Liver steatosis as one of the predictors of "non-response" to antiviral therapy for the treatment of chronic hepatitis C virus

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Introduction: It is considered that liver steatosis (LS) precedes nonalcoholic steatohepatitis which leads to cirrhosis. The usual flow of chronic hepatitis C (CHC) also leads to cirrhosis and liver cancer. An overlap of these diseases accelerates pathological process in several times. There is evidences of reduced effectiveness of the antiviral therapy (AVT) in those patients who have LS.

Methods: 84 patients with chronic hepatitis C with genotype 1, 2 or 3 HCV RNA and FLD (S0–S4). For verification of fibrosis, steatosis, inflammation, and alcohol or liver toxicity – Fibromax used. HCV RNA replication is determined by PCR together with genotyping and determination of viral load. To evaluate the effectiveness of the AVT used HCV RNA at the beginning of treatment and after 4, 12, 24 weeks therapy. Treatment outcomes successful (reach the sustained virologic response [SVR]) considered the absence of virus in the serum 24 weeks after the end of the AVT. Other necessary analyses also have been used. Patients were randomly divided into 2 groups. Group 1 (41 patients) used only the standard first line AVT (PEG-IFNα2a or PEG-IFNα2b combined with ribavirin), in Group 2 (43 patients) the 15 mg/kg UDCA for 12 weeks before and 12 weeks after initiation of treatment have been added.

Results: SVR was registered 29.2% of patients in Group 1 and 69.7% in Group 2.

Discussion/Conclusion:
– HCV can induce liver steatosis through varied, not yet full-elaborated mechanisms;
– LS reduces the effectiveness of AVT;
– identification of LS with HCV requires prescribing pathogenic treatment – UDCA.
Serotonin- and ghrelin-positive mast cells in human intestine in Crohn’s disease

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Introduction: Mast cells (MCs) are granular tissue cells with established role in a variety of pathologic processes including inflammatory bowel disease. They can release significant amounts of proinflammatory mediators, cytokines and growth factors. The role of MCs in Crohn’s disease is uncertain as they can participate in both inflammatory and reparative processes. The aim of the present study was to determine mast cells’ content of some inflammatory mediators in the intestinal wall in Crohn’s disease.

Methods: By the use of light microscopical immunohistochemistry and fluorescence co-localization we investigated histological preparations with Crohn’s disease from 6 patients, underwent surgical resection. MCs markers investigated are: tryptase (Try), chymase (Chy), c-kit, ghrelin (Ghr), substance P (SP), VIP, chromogranin (CHA), serotonin (SER) and somatostatin (SOM).

Results: In cases with active Crohn’s disease (3 cases) there was a significant increase of Try, c-kit, SP and VIP-positive mast cells as compared to inactive cases (3 cases). Something more in active disease there appeared SER+ and SOM+ MCs. For a second time we showed ghrelin positivity in mast cells. Fluorescence co-localization was done to confirm Try and Ghr; Try and SP; Try and VIP; Try and CHA-, Try and SOM positivity in mast cells. SER positivity in MCs was co-localized on serial sections with tryptase and toluidine blue.

Discussion/Conclusion: Human MCs in preparations from intestinal wall from patients with Crohn’s disease might secrete plenty of mediators which participate in the severe inflammation in active disease. Opposite to the general opinion that human MCs are SER negative we observed SER+ MCs in human intestinal wall.
The prevalence of alexithymia in inflammatory bowel disease: A systematic review and meta-analysis

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Introduction: Alexithymia is a dimensional personality trait, characterised by deficits in the cognitive processing and identification of emotions. Elevated rates of alexithymia have been observed in multiple chronic diseases, with detrimental moderating effects upon symptom experience, health-related quality of life and coping identified. Given the potential implications of alexithymia upon prognosis in inflammatory bowel disease (IBD), this study sought to systematically examine whether there is an increased prevalence and risk of alexithymia in IBD patients.

Methods: EMBASE, Medline, PsycINFO and Web of Science were systematically searched for cross-sectional, case-control and cohort studies using the Toronto Alexithymia Scale to report a prevalence or severity of alexithymia in IBD patients. Using the derSimonian-Laird random effects model, OpenMeta was used to calculate a pooled prevalence estimate for alexithymia in IBD patients. Using eligible case-control studies, random-effects models were used to calculate an odds-ratio for alexithymia in IBD patients compared to healthy controls.

Results: The systematic search yielded 343 unique texts and, of these, 12 and 10 studies satisfied criteria for inclusion in qualitative and quantitative analyses, respectively. In total, 1605 participants (52.0% male; mean age: 42.4 years) were included in the quantitative analysis. A pooled prevalence estimate for alexithymia in IBD patients of 34.1% (95% CIs: 21.0–47.1%) was calculated. Alexithymia occurred more commonly in patients with IBD versus healthy controls, with an odds-ratio of 7.6 (95% CIs: 4.4–13.3).

Discussion/Conclusion: This study demonstrates that there is a significant increase in the prevalence and risk of alexithymia in IBD patients versus the general population. Given the potential modifying effects that alexithymia may have upon symptom perception, health-related quality of life and other outcomes in IBD, further prospective studies examining alexithymia and its interaction with IBD are warranted.
Cardiovascular disease cases in patients with inflammatory bowel disease: Results of 7-year experience

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Introduction: Inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn’s disease (CD) are systemic, chronic inflammatory conditions and mainly affect the gastrointestinal tract. They also characterized by various extraintestinal manifestations.

Nowadays, it is evident that chronic systemic inflammation plays one of the principal roles in the pathogenesis of cardiovascular diseases (CVD).

Methods: 351 IBD patients were included in the study (UC = 266 and CD = 85), they were divided by sex and IBD subtype and their investigation results were compared to each other, also to healthy group (n = 362). All of them were non-smoker, without anamnesis of diabetes mellitus and other concomitant diseases, with normal BMI. The middle age was 51.5 ± 5.

Colonoscopy with biopsy was done for confirmation of diagnosis UC and CD. ECG, venous Doppler, CIMT (carotid intima-media thickness) test, lipids profile, all the biochemical parameters and additionally CRP, IL-6, TNF-α levels were estimated also for cardiovascular diseases’ risk assessment.

Results: Ischemic heart disease (IHD) cases (in 56 patients, 16%) – IBD patients, compared to healthy individuals, have an increased carotid intima-media thickness, a surrogate marker for IHD. No differences in risk were observed between sex and subtype of IBD. Examination showed an increased risk of myocardium infarct in IBD patients during flare (RR = 1.61; 95% CI: 1.21–2.14), whereas the risk was not increased during remission period (RR = 1.11; 95% CI: 0.92–1.27).

Venous thromboembolic events (VTEs) (in 28 patients, 8%) – No sex or IBD subtype differences were observed. More severe was inflammation the greater was risk of VTEs and it was much more prominent with a hazard ratio (HR) of 7.8 (95% CI: 4.9–11.3).

Cerebrovascular disease (CVD) – There was an increased risk of cerebrovascular disease in patients with CD, but not in UC patients (RR = 1.41; 95% CI: 1.15–1.74). Examination results showed a significantly increased risk of stroke among women with IBD compared to healthy controls (HR = 1.92, p < 0.05). During flares this risk was significantly increased (RR = 1.62; 95% CI: 1.31–2.01). Total number of patients with CVD was 7 (2%), 6 patients from them were from CD group and only one – from UC group.

Discussion/Conclusion: The risk of CVD is increased in IBD patients, particularly during flares. The elevated risk is most likely due to increased level of inflammatory mediators (CRP, IL-6, and TNF-α).

The cases of venous thromboembolic events in IBD patients may cause significant mortality, so antithrombotic prophylactic treatment is recommended for IBD patients. In the future, there is necessary to realize the true reasons and risk factors of CVD cases in IBD patients and their prevention.
The predictive value of ferritin in older patients in the diagnosis of colon cancer

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Introduction: Ferritin is an indicator of iron deficiency. However, it may produce false results in the presence of acute/chronic inflammation. In older patients, colon cancer is an important cause of morbidity and mortality. The aim of this study was to determine the predictive value of ferritin and ferritin-transferrin saturation combination for predicting the presence of colon cancer in older patients.

Methods: 600 patients aged > 65 years old were included into the study. Along with gastroscopic and colonoscopic findings, serum iron profile and C-reactive protein were also recorded. Patients were stratified into three groups according to their iron profiles: group 1: ferritin < 50 µg/l; group 2: ferritin < 100 µg/l; group 3: ferritin < 50 µg/l were the indicators for iron deficiency. If ferritin value was higher than 50 µg/l and transferrin saturation is below 16%, iron deficiency diagnosis was made.

Results: 528 patients had no upper and lower endoscopic findings that can result iron deficiency and 72 patients had colon cancer with normal gastroscopic findings. C-reactive protein values were found to be significantly high in the colon cancer group (p < 0.001). Ferritin value was found to be similar in the colon cancer and normal colonoscopy groups. In the colon cancer group, by means of showing the presence of iron deficiency; group 1 had 63% sensitivity and 53% specificity, group 2 had 79% sensitivity and 20% specificity, group 3 had 91% sensitivity and 49% specificity. In the ROC analysis, the AUROC value was found to be 0.704 for group 3. The patients in group 3 had significantly higher C-reactive protein values than the ones in group 1 and group 2.

Discussion/Conclusion: In older patients, normal ferritin values is not enough to disregard iron deficiency diagnosis. In this situation by using the transferrin saturation, a possible presence of iron deficiency should be investigated. Patients with transferrin saturation lower than 16% should undergo endoscopic examination with the diagnosis of iron deficiency.

References:
Systemic immune dysregulation has an impact on patients’ prognosis in the course of alcoholic liver injury

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Introduction: Recent evidence suggests that activation of innate immunity system and the subsequent inflammatory cascade play a central role in the pathogenesis of alcoholic liver disease (ALD). However, mechanisms of inflammation in ALD are still not completely understood. The aim of our study was to determine an impact of the Th17/Treg cell balance and its corresponding cytokine profile on the ALD outcome. Possible gender-related differences in the alcohol-induced inflammatory response were also assessed.

Methods: 147 patients with ALD were prospectively recruited, assigned to subgroups based on their gender, severity of liver dysfunction and presence of ALD complications, and followed for 90 days. Peripheral blood frequencies of Th17 and Treg cells, and IL-1β, IL-6, IL-17A, IL-23, and TGF-β1 levels were investigated. Flow cytometry was used to identify T cell phenotype and immunoenzymatic ELISAs for the corresponding cytokine concentration assessment. Multivariable logistic regression was applied in order to select independent predictors of advanced liver dysfunction and the disease complications.

Results: IL-17A, IL-1β, IL-6 levels were significantly increased, while TGF-β1 decreased in ALD patients. The imbalance with significantly higher Th17 and lower Treg frequencies was observed in non-survivors. IL-6 and TGF-β1 levels differed in relation to the patient gender in ALD group. Concentrations of IL-6 were associated with the severity of liver dysfunction, development of ALD complications, and turned out to be the only independent immune predictor of 90-day survival in the study cohort.

Discussion/Conclusion: Systemic immune dysregulation may have an impact on patients’ survival in ALD. IL-6 revealed the highest diagnostic and prognostic potential and was related to the fatal ALD course. Gender-related differences in the immune response might influence the susceptibility to ethanol-associated liver injury.
Hepatocellular carcinoma (HCC): Lessons learnt in the South East Coast UK-Royal Surrey County Hospital

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Introduction: The UK is facing an epidemic of liver disease of multimodal aetiologies, with end-stage disease and hepatocellular carcinoma (HCC) being increasingly reported. Biannual surveillance is recommended for cirrhotic and high-risk patients for early HCC diagnosis. Cytoreductive surgery and transplantation remain the only treatments with curative intent. Our tertiary hepatobiliary (HPB) centre serves 2.1 million patients in the South of England. We present our experience from 2010–2016 for patients who have been presented and managed in our regional HCC-MDT.

Methods: Patients were identified from records of MDT discussions, oncology/hepatology clinics and histology specimens; primary care datasets were reviewed where necessary.

Results: In the examined period, we managed 113 patients. A sevenfold increase has been observed in the last 12 months and 45 patients received treatment (median age 70). Approximately, 36% of patients were diagnosed histologically, whereas the remaining were diagnosed using a combination of tumour markers, imaging and clinical findings. Surprisingly, only 57% had cirrhosis. The commonest causes of liver disease were viral hepatitides, alcohol liver disease and non-alcoholic steatohepatitis. The mean overall survival (OS) was 12 months. Overall and disease-free survival for resection were 34 and 30 months respectively. This was significant compared to other treatment groups (p < 0.001). OS in cirrhotics vs. non-cirrhotics (10 vs.13 months) as well as differences in gender and age were not statistically significant. In the resected group, patients with more than one tumour survived 20 months less on average than those with multiple tumours.

Discussion/Conclusion: Our experience demonstrates a significant number of HCC resections in livers with histologically-normal or non-cirrhotic background, agreeing with reported rates of up to 40% in specific non-cirrhotic populations. Surgical resection should be offered to patients with compensated cirrhosis and advancing age given its curative intent and long-term outcomes. Our data shows widening HCC surveillance guidelines could capture these high-risk groups with early or no liver disease.
Helicobacter pylori infection influence on depression level in patients with functional dyspepsia

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Introduction: Helicobacter pylori-infection is associated with various gastroduodenal disorders ranging from functional dyspepsia (FD) to gastric cancer. Although the relationship between H. pylori and FD has been controversial, but treating H. pylori did have an effect in improving non-ulcer dyspepsia symptoms. Patients with FD are frequently found to be suffering from depression. It’s clear that there is a link between them.

Methods: The aim of study was to show if there is any relationship between H. pylori infection and depression level in patients with FD. 175 patients were included in the study (102 female, 73 male, mean age 27.5, range 19–35 years). FD was diagnosed according to the Rome Criteria III. H. pylori were identified by two methods, pursuant their instructions: 13C-urea breath test (13C-UBT) and stool test – H. pylori DNA in feces. Psycho-emotional status was estimated by hospital anxiety and depression scale (HADS).

Results: The results of H. pylori testing in 123 cases (70.3%) were negative (-) and in 52 cases (29.7%) positive (+). Patients with H. pylori(-) results had HADS score from 0 to 10, which is corresponded to normal (21 cases) and depression (102 cases) subscale, exactly subclinical expressed depression. All patients with H. pylori(+) results got HADS score 11 and above, which entirely estimated as a clinical expressed depression. Average HADS score for H. pylori(+) patients is 12.7 ± 0.35; which is significantly higher (p < 0.05) than average HADS score for H. pylori(-) patients – 8.17 ± 0.28.

Discussion/Conclusion: According to study, there is a correlation between H. pylori infection and depression level in patients with functional dyspepsia. On a background of H. pylori-negative test results there is no evidence of depression or there is its mild expression. But in cases of H. pylori-positive patients we had a real picture of clinical expressed depression. So H. pylori has an influence on the severity of depression level in patients with functional dyspepsia. In the future it’s necessary to examine which mechanism explains this fact.
Clinical features of isolated acute ischemic proctitis mimicking ulcerative proctitis

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Introduction: Acute ischemic proctitis seems to be rare because the rectum is usually spared in cases of ischemic colitis due to the extensive collateral network. In outpatients, isolated rectal inflammation may be endoscopically confused with ulcerative proctitis. Herein, we reviewed the ten cases of ischemic proctitis and analyzed their clinical characteristics.

Methods: We retrospectively investigated the patients who were clinically diagnosed with ischemic colitis at Daehang hospital from 2005 January to 2015 December. Among 206 patients with ischemic colitis, the ten cases (4.9%) in which the disease extent was localized just in the rectum were included. Patient demography, presenting symptom, underlying chronic illness including constipation were analyzed.

Results: Of a total of ten patients who were diagnosed with isolated acute ischemic proctitis, seven were male (70%), and median age was 62 (33–79) years old. All were outpatients. The patients showed hematochezia in seven (70%), abdominal pain in three (30%). Seven patients had hypertension (70%), three patients had diabetes (30%), and six patients had chronic constipation (60%). Two cases developed after medical diagnostic procedures (one, after colonoscopy; the other, after trans-anal sonography). In all patients, rectal inflammation improved completely on short-term follow-up sigmoidoscopy.

Discussion/Conclusion: Isolated ischemic proctitis should be distinguished from ulcerative proctitis. It can develop especially in the elderly patients with underlying chronic illness such as hypertension or chronic constipation in the setting of outpatient clinic.
The effectiveness of treatment of patients with luminal form Crohn's disease mesenchymal stromal cells of the bone marrow: 7 years of observation

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Anticytokine therapy with anti-TNF-α drugs contributes to the achievement of stable remission of Crohn's disease (CD). For the treatment of CD are also using mesenchymal stromal cells (MSCs).

Objective: To examine the long-term efficacy (7 years) therapy mesenchymal stromal cells (MSCs) from the bone marrow of patients with luminal Crohn's disease (CD).

Materials and Methods: 80 patients with luminal form CD (terminal ileitis, colitis and ileocolitis) were divided into two groups. The first group of patients aged 19–58 years old (Me-29) (n = 34) received the culture of MSCs under the scheme (0-1-2-3, then every 26 weeks). The second group of patients with CD (n = 46) aged 20–62 years old (Me-28) received standard anti-inflammatory therapy with 5-aminosalicylic acid (5-ASA), glucocorticosteroids (GCS) and immunosuppressives (IS). Evaluation of the effectiveness of therapy on the level of the index of activity of Crohn's disease (CDAI) was carried out at 12, 24, 36, 48, 60, 72 and 84 months after initiation of therapy.

Results: Among the patients in 1st group relapse in the 12 months of observation occurred in 4/36 patients (11.76%). In 2nd group, relapse occurred in 5/46 (10.8%) (p = 0.82). After 24 months in the 1st group of patients receiving MSC, relapse occurred in 6/34 (17.6%). In the 2nd group of patients relapse in 19/27 (41.3%) (p = 0.044). After 36 months in 1st group patients with a relapse of the disease in 11/34 (32.3%). In the 2nd group relapse 29/46 (63.1%) (p = 0.01). After 48 months in 1st group, receiving MSCs, relapsed in 15/34 (44.1%). In the 2nd group relapse of the CD in 33/46 (71.7%) (p = 0.023). After 60 months in the 1st group relapse in 19/34 (55.9%). In the 2nd group relapse 40/46 (86.9%) (p = 0.004). After 72 months in 1st group relapse 25/34 (73.5%). In 2nd group relapse of the CD in 45/46 (97.8%) (p = 0.001). After 84 months in 1st group relapse CD in 29/34 (85.3%). In the 2nd group of patients CD relapse occurred in 46/46 (100.0%) (p = 0.011).

Conclusions: MSCs transplantation helps to maintain a long-term clinical remission in patients with luminal Crohn's disease compared with GCS/IS therapy.
Combination therapy of bone marrow mesenchymal stromal cells and azathioprine not affect the clinical course luminal Crohn's disease

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New treatments for Crohn's disease (CD) is a biologic therapy using mesenchymal stromal cells (MSCs) of the bone marrow. In some cases, together with the MSC, patients receiving concomitant immunosuppressive therapy. It is found that immunomodulatory drugs (azathioprine, methotrexate, 6-mercaptopurine, infliximab [IFX]), regardless of the concentration, do not affect the viability, differentiation, phenotype, and ability to inhibit proliferation of MSCs peripheral blood mononuclear cells [1]. However, studies conducted by Huang HR, et al. It demonstrates that IFX rendered minimal impact on the MSC proliferation, apoptosis and cell cycle, while, azathioprine inhibited cell proliferation and induced apoptosis of MSCs in vitro [2].

The aim of our work was to study the effect of the combined use of bone marrow MSCs and azathioprine (AZA) on the clinical course of CD.

Materials and Methods: 34 patients with BC luminal form divided into two groups. The first group of patients aged 19–58 years old (Me-29) (n = 15) was treated with anti-inflammatory therapy with MSCs culture 2 million cells/kg + AZA 2 mg/kg. The second group of patients with CD (n = 19) aged 23–60 years old (Me-31) received MSCs according to the recommended scheme (without AZA). Culture MSCs were injected three times a month at intervals of 1 week after 6 months from the date of the first administration of MSCs. The initial average index of activity of Crohn's disease (CDAI) in the first group amounted to 337.6 ± 17.1 points, the second group 332.7 ± 11.0 points (p = 0.3). Evaluation of efficacy was performed at 12, 24 and 36 months.

Results: After 12 months in the first group of patients relapse occurred in CD 1 (6.6%) patient, the second in 2 (10.5%) (OR = 0.63; 95% CI: 0.06–6.34, p = 0.82). Middle CDAI in the first group of patients 99.9 ± 10.8 points, the second 100.6 ± 12.1 points (p = 0.8). After 24 months in the first group of patients with relapsed CD occurred in 3 patients (20.0%), the second in 4 (21.05%) (OR = 0.95; 95% CI: 0.25–3.61, p = 0.72). Middle CDAI in the first group of patients with CD was 133.2 ± 28.3 points, the second 120.8 ± 15.5 points (p = 0.2).Through 36 months in the first group of patients with CD relapse occurred in 5 (33.3%) patients with CD, the second in 6 (31.6%) (OR = 1.06; 95% CI: 0.4–2.8, p = 0.79). Middle CDAI in the first group of patients with CD was 139.9 ± 23.4 points, the second 141.7 ± 20.8 points (p = 0.9).

Conclusion: During three years of follow up in patients treated with MSCs and AZA, and in patients receiving only MSCs, there was no difference in the frequency of relapses and CD clinical activity.
References:

Supplementation of probiotic strains with nutraceuticals differentially affects manifestation of experimental NAFLD

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Introduction: Today probiotics have been suggested as a treatment for the prevention of non-alcoholic fatty liver disease (NAFLD). Omega-3 fatty acid treatment may have beneficial effects in regulating hepatic lipid metabolism, adipose tissue function, and inflammation. Smectite is a natural silicate that has the ability to bind endo- and exotoxins, increased water and electrolyte absorption and restored the barrier properties of human intestinal cell monolayers.

The study aims to determine whether probiotics plus nutraceuticals such as smectite or n3-PUFA are superior to probiotic alone on the monosodium glutamate (MSG) induced NAFLD model in rats.

Methods: Totally 75 rats divided into 5 groups were included (n = 15, in each). Rats of group I were intact. Newborn rats of groups II–IV were injected with MSG. The III (Symbiter) group received 2.5 ml/kg of multiprobiotic "Symbiter" containing concentrated biomass of 14 probiotic bacteria genera. The IV (Symbiter-Omega) and V (Symbiter + Smectite) groups received combination of probiotic biomass supplemented with flax and wheat germ oil (250 mg of each, concentration of omega-3 fatty acids 1–5%) or smectite gel (250 mg) respectively.

Results: In all interventional groups reduction of total NAS score was observed. Supplementation with omega 3 fatty acids lead to 20% higher decreasing of steatosis score (0.73 ± 0.11 vs. 0.93 ± 0.22, p = 0.848) and reduction by 16.6% of triglycerides content in liver as compared to probiotic alone. Co-treatment with Symbiter + Smectite are associated with more pronounced reduction of lobular inflammation (0.13 ± 0.09 vs. 0.33 ± 0.15).

Discussion/Conclusion: Our study demonstrated more pronounced reduction of steatosis and hepatic lipid accumulation after treatment with combination of alive probiotics and omega-3 as compared to probiotic alone. Supplementation with smectite gel due to his absorbent activity and stabilization mucus layer properties can impact on synergistic enhancement of single effect which manifested with reduction of lobular inflammation and at list partly NASH prevention.
Immunological status, endotoxemia and dysbiosis in patients with type 2 diabetes and non-alcoholic fatty liver disease

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Introduction: The leading role in the development of T2DM and NAFLD belongs to immunopathological mechanisms that determine the nature of the flow in the future of this pathology, the rate of propagation and severity of specific complications. The aim of the study is to find changes of cytokine status and major lymphocyte subpopulations, endotoxiaemia and microbiota of patients with T2DM and NAFLD.

Methods: We have observed 64 patients with T2DM and NAFLD and 25 apparently healthy individuals (control group). The concentration of cytokines (interleukin [IL]-6, -8, TNF-α) in blood serum and coprofiltrates, Ig to lipopolysaccharide (LPS) in blood serum were determined by ELISA. The lymphocyte subpopulations composition was studied by flow cytometry “FC-500”. The state of intestine microbiota was evaluated based on the results of bacteriological examination of feces.

Results: In patients with T2DM and NAFLD were marked increased levels of pro-inflammatory cytokines in blood serum and coprofiltrates. We also revealed imbalance in the composition of lymphocyte subpopulations, observed by decreased blood levels of CD8+ and CD16+ cells at a stable level of T helper (CD4+) cells and increased content of CD20+ cells. In patients T2DM with NAFLD was registered an increased apoptotic readiness of lymphocytes, which revealed by increased CD95+ cells in the blood. The relationships (Spearman’s rank correlation coefficient, \( r \neq 0 \) at \( p < 0.05 \)) were detected between the dysbiosis rate and cytokine production in coprofiltrates of examined patients: for TNF-α – \( r = 0.538 \); for IL-6 – \( r = 0.528 \); for IL-8 – \( r = 0.586 \). We discovered straight correlation between TNF-α, IL-6 and IgG to LPS in patients with DM2 and NAFLD (TNF-α and IgG to LPS, \( r = 0.67 \); IL-6 and IgG to LPS, \( r = 0.56 \)) that indicates the specific role of endotoxins of Gram-negative flora in systemic inflammation induction in this pathology.

Conclusions: The analysis of patients with T2DM and NAFLD has marked significant increase in the concentration of pro-inflammatory cytokines in blood serum and coprofiltrates, depending on the intestine dysbiosis and IgG to LPS rate indicating that a significant inflammatory and immunopathological reactions form base for this disease. We also consider that dysbiosis correction may improve immunological status in this patients.
DIOS syndrome in 11-month-old infant with cystic fibrosis

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Introduction: Syndrome DIOS in patients with cystic fibrosis (CF) occurs with frequency of 6.2/1000 patients/year, mainly in adolescents and young adults. Extremely rare in younger children. To know risk factors include the DIOS: meconium obstructions in the neonatal period, abnormal enzyme supplementation, dietary errors, dehydration, use of drugs regulating intestinal peristalsis, increased changes in the airways, previous lung transplantation.

Objective: Analysis of the clinical assessment of risk factors DIOS syndrome in 11-month-old infant suffering from CF.

Material and Methods: Presented a case of DIOS in 11-month-old female infant diagnosed with CF newborn screening test. Baby handed over to the district hospital because of febrile conditions, reduction to drink fluids and eating, ion disorders. On admission the child had features of dehydration and bloated belly with lazy motility. In additional studies: high rates of inflammation, electrolyte disturbances, hypoproteinemia, high rates of acidic steatocrit. Despite the persistence of observed treatment of infections parameters, growth of abdominal circumference, disposable vomiting. The diagnostic imaging studies, including the intestinal passage showed retention of contrast around the ileocecal bowel. Child consulted surgery. Oral feeding was stopped, was used rectal infusions of N-acetylcysteine, irrigation, included metronidazole, standard realimentation with enzyme supplementation. Improvement in clinical status was obtained.

Conclusions:
1. Avoidance and effective treatment of states of dehydration and the proper enzyme supplementation may reduce the risk of DIOS syndrome in infants.
2. Coexistence several risk factors in the same child greatly increases the risk of developing ovarian DIOS.
Bile acids regulate intestinal wound healing by FXR-mediated inhibition of CFTR expression in human colonic epithelial cells

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Introduction: Epithelial restitution is an essential process for maintenance of intestinal barrier function. Increased levels of colonic bile acids have been proposed to be involved in the pathogenesis of inflammatory bowel disease (IBD) but their roles in regulating restitution are not yet known. Here, we investigated the effects of bile acids on epithelial restitution and molecular pathways involved in colonic epithelial healing.

Methods: T84 colonic epithelial cells, grown as monolayers on transparent permeable supports, were wounded by scratching with a pipette tip at T = 0. Cells were treated with either the most abundant colonic bile acid, deoxycholic acid (DCA; 150 µM), the “therapeutic” bile acid, ursodeoxycholic acid (UDCA; 100 µM), a farnesoid X receptor (FXR) agonist, GW4064 (5 µM), or a cystic fibrosis transmembrane conductance regulator (CFTR) channel blocker, CFTR(inh)-172 (10 µM). Restitution was measured as wound area after 48 h expressed as % T = 0 wound area. HEK-293 cells were transfected with vector expressing luciferase gene under control of the CFTR promoter and vectors expressing FXR. Protein expression was assessed by western blotting and cell migration by Boyden chamber assay.

Results: After 48 h post-wounding, wound closure in untreated cells was 63.3 ± 13.5% of that at T = 0, while in cells treated with DCA (150 µM) it was reduced to 24.5 ± 13.1% (n = 5; p < 0.001), whereas UDCA enhanced healing to 88 ± 4 (n = 5; p < 0.001). Furthermore, UDCA prevented inhibition of wound closure by DCA. The effects of DCA are mediated via a decrease in cell migration to 0.7 ± 0.1 fold (n = 5, p < 0.05) of that in untreated controls, rather than inhibition of cell growth. Furthermore, DCA decreased cell surface CFTR expression to 23 ± 5% of controls (n = 3, p < 0.001), while a CFTR inhibitor, CFTR(inh)-172 (10 µM), attenuated wound closure to 37 ± 2% (n = 5; p < 0.01), compared to control. Moreover, DCA decreased CFTR promoter activity, in a concentration-dependent manner that was also dependent on co-expression of FXR. Finally, GW4064 (5 µM), an agonist of FXR, mimicked DCA effects on wound healing and CFTR expression.

Discussion/Conclusion: Our data suggest that colonic bile acids differentially regulate intestinal epithelial restitution and that UDCA promotes healing and protects against the detrimental effects of DCA. Thus, manipulation of the colonic bile acid pool may prove to be a useful approach for promoting intestinal barrier function in IBD.
Bile acids regulate colonic epithelial defensin secretion: Implications for pathogenesis and therapy of inflammatory bowel disease

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Introduction: Increased secretion of colonic epithelial human β defensins (HβDs) has been proposed to contribute to the pathogenesis of ulcerative colitis (UC) through induction of chemokines and the consequent infiltration of mucosal immune cells. Although alterations in the colonic bile acid pool also occur in UC, the roles of bile acids in regulating HβD production are not yet known. Here, we investigated the effects of two common colonic bile acids on epithelial HβD release; deoxycholic acid (DCA), the most common of the colonic bile acids, and ursodeoxycholic acid (UDCA), which we and others have shown to exert anti-inflammatory actions in vivo.

Methods: HβD release from monolayers of T84 colonic epithelial cells or muscle-stripped sections of human colon mounted in Ussing chambers were measured by ELISA after treatment with DCA (10–150 µM) or UDCA (50–100 µM). Colonic mβD-1 and mβD-4 mRNA levels from WT and TGR5-/- mice were measured by q-PCR. Use of human and mouse tissue was approved by the Beaumont Hospital Ethics Committee.

Results: DCA significantly increased HβD-1 and HβD-2 secretion from T84 cells from 190 ± 28 pg/ml to 413 ± 34 pg/ml and 27 ± 5 pg/ml to 291 ± 2 pg/ml (n = 4; p < 0.01), respectively. Furthermore, UDCA attenuated DCA-stimulated HβD-1 and HBD-2 release to 82 ± 10 pg/ml and 95 ± 17 pg/ml, respectively (n = 4; p < 0.05). Similar effects were seen in ex vivo sections of distal human colon. Similar to DCA, (INT-777, 10 µM) a specific agonist of the bile acid receptor, TGR-5, stimulated both HβDs release from T84 cells and these responses were significantly reduced by UDCA treatment. INT777 (30 µM) failed to increase levels of mβD-1 and 4, orthologues of HβD-1 and 2, respectively, in TGR5-/- but not in WT mice. Finally, a specific inhibitor of NF-κB, BMS-34451 (25 µM) attenuated DCA (150 µM)-induced HβD-2, but not HβD-1, secretion to 27 ± 8 pg/ml (n = 6; p < 0.01).

Discussion/Conclusion: Taken together our data suggest that DCA, likely through activation of TGR5, promotes colonic epithelial HβD secretion. In contrast, UDCA inhibits HβD secretion, an effect which may underlie its anti-inflammatory actions in vivo. Thus, alterations in colonic bile acid pool may influence UC pathogenesis through alterations in HβD production.
The potential of secreted molecules of human amniotic fluid mesenchymal stem/stromal cells in IBD therapy

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Introduction: Inflammatory bowel diseases (IBDs) are the result of pathological immune responses to environmental factors/microbial antigens to a genetically predisposed individual. There is a growing interest in the therapeutic potential of human mesenchymal stem/stromal cells (hMSCs) in IBD disease animal models which is mostly due to their trophic factors. The purpose of this study was to research a new approach for IBD MSC-based therapy though looking at the potential of a specific population of second trimester amniotic fluid mesenchymal stem/stromal cells and spindle-shaped MSCs (SS-AF-MSCs).

Methods: Dextran sulphate sodium (DSS) (3% w/v in tap water) was orally administered to NOD/SCID mice, approximately 8 weeks old, for 5 days to induce colitis. The progression of the colitis was assessed daily through monitoring body weight, stool consistency and bleeding. A SS-AF-MSCs conditioned media was collected and concentrated before being injected intraperitoneally. Inflammatory cytokine levels were then determined through carrying out histopathological analysis.

Results: Results showed that the CM derived from SS-AF-MSCs cells reduced the severity of colitis in mice who were administered the CM. TNFα and MMP2 protein levels were decreased in these mice whereas TGFβ1 protein levels were increased. The anti-inflammatory cytokine IL-10 had a substantial increase in mice that were given the CM, however, TNFα and IL-1β were decreased at mRNA level.

Discussion/Conclusion: The results obtained showed that SS-AF-MSCs derived CM is able to improve DSS-induced colitis in immunodeficient mice models and thus could be a potential therapeutic approach for IBD treatment.
Condition of immune response to lipopolysaccharides of gut microbiota in chronic viral hepatitis and liver cirrhosis

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Objective: To study a condition of the innate and adaptive immune response to endotoxins of gut microbiota in chronic viral hepatitis (CVH) and the viral liver cirrhosis (VLC).

Material and Methods: The concentration anti-endotoxin antibodies (AEA), lipopolysaccharide binding protein (LBP) and soluble form of cluster of differentiation 14 (sCD14) in the blood plasma were determined in 49 CVH patients, 60 VLC patients and 30 healthy donors (HD) by ELISA using the test systems of “Hycult Biotech” (Netherlands).

Results: Mean AEA concentration in HD was 8.0 ± 0.38 μg/ml, in CVH-8.54 ± 1.24 μg/ml, in VLC-10.0 ± 1.14 μg/ml. The level of AEA in HBV positive patients with VLC was 11.67 ± 1.33 μg/ml versus 8.0 ± 0.75 μg/ml in HCV positive patients. Statistically significant correlation (r = 0.444) between increased AEA level and HBV markers was determined. There was similar trend in HCV markers but not significant. Mean LBP concentration in HD was 13.5 ± 0.9 μg/ml, in CVH 33.2 ± 2.3 μg/ml, in VLC 39.0 ± 1.5 μg/ml (λ² = 18.0, p = 0.001). sCD14 concentration in HD was 2.7 ± 0.3 μg/ml, in CVH-4.9 ± 0.1 μg/ml, in VLC-5.2 ± 0.2 μg/ml (λ² = 15.2; p = 0.002). Correlation coefficient between concentration of LBP and sCD14 was r = 0.35 in CVH and r = 0.42 in VLC, that reflects more close interaction among this parameters in liver process progression and development of portal hypertension. Comparison of mean values of sCD14 and LBP concentration depending on the availability of HBV or HCV markers in blood did not reveal significant differences. Despite the lack of statistical significance, average LBP level in HCV-positive patients with CVH and VLC was slightly higher than in HBV positive patients (34.9 ± 1.4 μg/ml vs. 31.5 ± 1. μg/ml in CVH and 41.6 ± 1.5 μg/ml vs. 36.4 ± 1.7 μg/ml in VLC). Mean values of sCD14 in patients with CVH and VLC were practically independent from the type of hepatotropic virus.

Conclusion: The significant increase of AEA, LPB and sCD14 was determined in patients with CVH and VLC. On the one hand, it shows the severity of endotoxemia syndrome and bacterial overgrowth, and on the other the activation of innate and adaptive immune response to endotoxins of gut microbiota.
Initial infliximab treatment efficacy without previous conventional therapy in patients with moderate-to-severe ulcerative colitis

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Introduction: Anti-TNFα that used in patients with moderate to severe UC who are either refractory to or intolerant to conventional therapy (CT) with 5-ASA and corticosteroids. The aim was to evaluate the infliximab (IFX) efficacy for treating patients with moderate-to-severe UC without using previous CT.

Methods: Total 53 patients with moderate-to-severe established UC were divided into two groups: Group 1 (27 patients) never received CT for UC. Group 2 (26 patients) were treated with 5-ASA and corticosteroids only, but have not achieved remission or got relapse after CT. All the patients were naïve to IFX. To evaluate the efficacy all subjects underwent colonoscopy, laboratory evaluation, questionnaires before and after treatment. The disease activity and relapse on treatment of IFX at week 8 were measured. The follow-up period was 1 year.

Results: 1) Group 1 received IFX 5 mg/kg 0, 2, 6 week. Before treatment the mean score (MS) of Clinical Activity Index (CAI) was 9.43 ± 0.64 points and the MS of Endoscopic Index (EI) was 8.1 ± 0.56 points. After treatment, 22 patients (81.4%) achieved stable remission (p < 0.05). Other 5 patients (18.6%) got better clinical and endoscopic indicators, CAI MS decreased to 5.20 ± 0.30 points and EI MS became 4.13 ± 0.31 points that meet mild UC activity (p < 0.001). After treatment, the number of patients with abnormal laboratory values was decreased (p < 0.05). 2) Group 2 received IFX 5 mg/kg 0, 2, 6 week. Before treatment CAI MS was 9.43 ± 0.40 points and EI MS was 8.87 ± 0.34 points. As a result 22 patients (84.6%) achieved stable remission (p < 0.05). Other 4 patients (15.4%) got better clinical and endoscopic indicators, CAI MS decreased to 4.63 ± 0.51 points and EI MS became 4.27 ± 0.39 points that meet mild UC activity (p < 0.001). Laboratory markers were decreased (p < 0.05).

Discussion/Conclusion: The results allow suggest that is more expediently to initiate the treatment of UC with anti-TNFα, and when the remission will be achieved – to prescribe the 5-ASA for the prolongation of the remission.
Introduction: Lack of complete epidemiological data about prevalence of infection with hepatitis D virus in patients with chronic hepatitis B may lead to delay in diagnosis and antiviral therapy. We present two cases of co-infection with HDV, hepatitis B and C viruses.

Methods: Retrospective, demographic and clinical data were collected for both patients from medical records in Pomeranian Center of Infectious Diseases in Gdansk, from 2002–2016 years.

Results: Both male patients were primarily diagnosed as infected with HBV and HCV, HBsAg-positive and anti-HCV-positive. The first patient with HCV replication received 48 weeks of treatment with interferon and ribavirin. Despite of sustained viral response (HCV RNA-negative) he developed severe exacerbation of hepatitis with active HBV replication and rapid progression of necroinflammatory activity and fibrosis in liver biopsy. Treated with lamivudine he achieved undetectable HBV DNA without improvement in aminotransferases activity. The detection of anti-HDV and HDV RNA confirmed infection with HDV. The patient was treated twice with pegylated interferon. Transient, significant reduction of aminotransferases activity was observed without anti-HDV viral response. In the USG elastography progression of liver fibrosis to F4 was described.

The second patient, HCV RNA-negative, presented severe chronic hepatitis with low HBV viral load, hemosiderosis. During interferon treatment liver function tests transiently improved. The next therapy with lamivudine was ineffective. Rapid progression of liver fibrosis was observed. After the detection of anti-HDV and HDV RNA the patient received pegylated interferon. A full virological and biochemical response was achieved.

Discussion/Conclusion: HDV infection should be considered in patients with low replication rate of HBV, high inflammation activity despite of a good virological response to anti-HBV treatment. Efficacy of interferon therapy in HDV infection is significantly limited. Coinfection with HDV in CHB associates with a risk of rapid progression to liver cirrhosis.
Co-morbidities in inflammatory bowel disease patients

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The prevalence of co-morbidities in patients with inflammatory bowel disease (IBD) is high. The most common extra-intestinal manifestation of IBD was anemia due to chronic blood loss, concomitant disease – non-alcoholic fatty liver disease (NAFLD).

Introduction: Important factor such as co-morbidity must be considered when making clinical decisions in patients with IBD. On the other hand quality of life is closely related to amount and severity of concomitant diseases.

Methods: We reviewed the medical records of 71 inpatients with ulcerative colitis and 2 patients with Crohn’s disease who were followed at a Gastroenterology Department of Gomel Clinical Hospital (Belarus) between January 2014 and February 2016. Personal data, clinical, laboratory, endoscopy, histology parameters, abdominal imaging were analyzed.

Results: 56 middle-aged (41.1 ± 15.9 years old, 48% men) IBD patients were included. The mean age at diagnosis of IBD was 38.7 years. 2 women were pregnancy. Extra-intestinal manifestations of IBD revealed in 39.3% patients and include anemia (35.7%), erythema nodosum (3.6%), pyoderma (3.6%), arthritis (5.4%), rarely (on 1.8%) – primary sclerosing cholangitis, autoimmune thyreoiditis, nephrolithiasis, scleritis. Laboratory investigations revealed leukocytosis (44.6%), thrombocytosis (19.6%), which may be associated both with disease activity and iron deficiency anemia. Concomitant diseases include NAFLD – in 19.6%, diabetes mellitus – 14.3%, nephritis – 12.5%, pancreatitis – 8.9%, peptic ulcer disease – 8.9%, arterial hypertension – 12.5%, ischemic heart disease – 5.4%, hypothyroidism – 3.6%, myasthenia gravis – 1.8% patients.

Discussion/Conclusion: Co-morbidities is a common pathology and revealed in 71.4% among IBD patients. Anemia is the most frequent extra-intestinal manifestation of IBD, affecting approximately one third of patients. NAFLD affect one fifth of patients and may complicate treatment decisions, influence pharmaceutical choices, and potentially predispose IBD patients to develop fibrosis and cirrhosis.
Lactoferrin as a biomarker in liver cirrhosis patients with bacterial infections

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Lactoferrin can be the potential biomarker for faster diagnosis, monitoring the disease course, predict exacerbations and improve the management urinary tract infections (UTI).

**Introduction**: Bacterial infections are important factors in decompensation patients with liver cirrhosis. In recent years the use of biomarkers has been evaluated in the diagnosis and management of inflammatory diseases.

**Methods**: Concentrations of lactoferrin in the serum, urine, ascitic fluid by enzyme immunoassay were measured from age- and sex-matched patients with liver cirrhosis from prospective study. Diagnosis of UTI was made based on laboratory data (≥ 10 leukocytes/mm³ in urine and/or positive uroculture, bacteriuria ≥ 10⁵ cfu/ml).

**Results**: 100 middle-aged (51.1 ± 11.9 years old, 57% men, 43% women) cirrhotic inpatients Child-Pugh criteria A/B/C (11/43/46) were included. 40 (40%) were admitted with an UTI, 18 (18%) – pneumonia, 3 (3%) – spontaneous bacterial peritonitis. The level of lactoferrin in serum and ascitic fluid had no significant difference between patients with/without pneumonia and spontaneous bacterial peritonitis respectively (p > 0.05). The concentration of lactoferrin in urine was significantly higher among patients with UTI (611.7 ng/ml, 95% CI: 347.2–1570.7) comparing patients without UTI (33 ng/ml, 95% CI: 14.1–52.0) (p = 0.0037). Revealed association between level of leucocytes and concentration of lactoferrin in urine (R = 0.37, p = 0.002).

**Discussion/Conclusion**: UTI is common in patients with advanced liver disease and occurs in approximately 40% of the cases. To determine the level of lactoferrin in urine can be considered as an additional test for the diagnosis of UTI. This biomarker can help of the standard methods in the screening for asymptomatic bacteriuria and will allow prescribe antibacterial therapy as soon as possible to prevent the development of clinically significant UTI.
Treatment of small cell stomach MALT lymphoma

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Aim: To study the efficiency of combined therapy with small cell MALT lymphoma of the stomach (SC-MALTS).

Materials: We analyzed the treatment results of 75 patients with MALTS, average age of 44.7 ± 0.4 years. Men was - 26 (35.3%), 47 women (64.7%). A comparative study of the macroscopic type of tumor in 34 (45.3%) found infiltrative ulcer, 27 (36.0%) - peptic ulcer, 14 (18.7%) - a form of infiltrative growth. Histological verification of small-cell type of tumor found in 35 (46.7%) patients, intermediate type - in 25 (33.3%) and in 15 (20.0%) - multi-mixed type lymphoma of the stomach. By classification of Lugano (1993) 1st stage in 49 (65.3%) patients, IIE - in 10 (13.3%), II1 - in 11 (14.6%), II2 - 5 (6.6%). Availability gastroenterological diseases in history was observed 54 (72.0%) patients. In particular, SC-MALTS it occurred in 21 (60.0%) patients with a history of 3-month duration (9 patients) and 5 years (5 patients). The involvement of the body of the stomach was most characteristic of SC-MALTS - 19 (54.3%) patients, total affection were - in 9 (25.7%), the involvement of the distal portions of the stomach - in 7 (20.0%). In 29 (82.8%) in the examination revealed the presence of infection with Helicobacter pylori (Hp) different degrees of contamination. However, from the min 13 (37.1%) patients due to the presence of functional gastric complications (bleeding and stenosis) being performed gastrectomy with lymph node dissection to D2. Postoperatively, these patients underwent adjuvant chemotherapy (ChT) by the schedule of ELF. 6 (17.1%) (Hp-negative) patients were only ChT, the remaining 16 (45.8%) patients (Hp-positive) was performed ChT with anti-Hp therapy (triada therapy).

Results: In the postoperative period in patients with SC-MALTS complications was not observed. After ChT all 6 (100%) patients observed side effects of chemotherapy I- and II-toxicity that stopped inclusion arsenal treatment of symptomatic therapy. After chemotherapy with anti-Hp therapy in 1 (5.5%) patient the presence of side-effects of chemotherapy I-toxicity. Indices of one-year survival rate in the groups were identical at 100% (p > 0.05). However, the performance of 3-year survival rates were slightly different, accounting for 84.6, 66.6 and 87.5%, correspondingly (p > 0.05). Patients after surgery + ChT and ChT + anti-Hp therapy during the observation period 3 year recurrent disease is not established. After the chemotherapy of 6 patients in 5 (%) marked relapse during 13 to 28 months that required repeated the courses of chemotherapy with the inclusion of anti-Hp therapy.

Conclusion: The analysis shows the appropriateness of an integrated approach in the treatment of MALTS. Thus, performance of surgical component, followed by using of adjuvant chemotherapy does not degrade performance of remote results. Application of anti-Hp therapy in these patients in conjunction with chemotherapy to achieve the most optimal remote results, indicating the need for inclusion in the arsenal of therapeu tic measures in SC-MALTS.
Quality improvement project: Cost saving through switching 5-ASA (aminosalicylic acid) drugs in ulcerative colitis patients in clinical remission

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Introduction: Ulcerative colitis (UC), a chronic inflammatory condition of the bowel, affects 1% of the UK population. The first-line treatment is mesalazine [1], a 5-aminosalicylic acid (5-ASA). A recent Cochrane Systematic Review [1, 2] concluded that there was no significant difference in efficacy or safety between 5-ASA formulations in maintaining UC remission from their current 5-ASA drug to a cheaper yet effective alternative.

Methods: A database of UC patients, taking 5-ASA, attending St. Peter’s Gastroenterology Outpatients between 2014 and 2016 was collated retrospectively. Patients in clinical remission, defined by a Mayo score > 2, were categorised by the 5-ASA formulation they were prescribed. The cost of maintenance treatment per year for each 5-ASA formulation was calculated against the alternative formulation.

Results: 200 of 304 patients were identified as being in clinical remission. 100 patients were on Asacol®, 96 on Octasa®, 2 on Pentasa®, 2 on unknown brands and none on Salofalk® granules. Based on MIMS April 2015, the current yearly cost for the 198 patients in remission is £127,790. The cost if on Salofalk® granules would be £58,608, a cost saving of £69,182 (54.1%).

Discussion/Conclusion: There is a significant potential cost saving by switching 5-ASA formulations for patients with UC in clinical remission. In today’s climate of reduced spending in public health, such a cost saving could be reinvested into needed services such as a second inflammatory bowel disease nurse.

A limitation of this project is addressing the patient perspective of changing medical therapies. Patients in clinical remission whose current therapy works for them could be reluctant to change to a new therapy. This project was also not designed to consider the associated costs of changing prescribing practices.

References:

The diabetic enteropathy treatment optimization in patients with type 2 diabetes in combination with the bacterial overgrowth syndrome

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In recent decades, an incidence increase in the diabetes mellitus (DM) type 2 is observed, which is often accompanied by secondary complications in forms of micro- and macroangiopathy and polyneuropathy, which leads to polysystemic complications. Diabetic enteropathy (DE) is formed on the background of the motor-evacuation function violations of the gastrointestinal tract (GIT) and can be accompanied by syndrome of intestine bacterial overgrowth (SIBO).

The aim: To determine the SIBO role in endothelial dysfunction potentiation in patients with DM type 2 with DE.

Materials and Methods: The study involved 187 patients with DM type 2 with DE, 79 (42.3%) men, 108 (57.7%) women, average age 56.9 ± 8.41 years, the duration of the type 2 DM was 7–10 years. DM type 2 was in the subcompensation stage: HbA1c level ≤ 7.5%, without ketoacidosis. Carbohydrate metabolism was corrected using the combined hypoglycemic therapy. The hydrogen breath test with lactulose was performed, according to its results patients were divided into 2 groups: (n = 126) – patients with DM type 2 combined with SIBO; II (n = 61) – patients with DM type 2 without SIBO. The total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C; alanine (ALT), aspartic (AST) aminotransferase, γ-glutamyltranspeptidase (GGTP), alkaline phosphatase (ALP), total bilirubin were determined. The levels of nitrites and nitric oxide synthase (NO-synthase) total activity were evaluated.

Results: In patients with DM type 2 of the group I the atherogenic dyslipidemia was found, which was characterized by the increased levels of cholesterol in 1.36 times, LDL-C in 1.41 times, TG 2.48 times in a simultaneous decrease of the HDL-C in 1.41 times compared to normal (p < 0.05). In group II patients without violations of the small intestine microbiota a reliable TG increase in 1.9 times was noted compared with the healthy individuals (p < 0.05). The SIBO presence was accompanied by functional liver disorders, that were characterized by the increased activity of ALT in 2.4 times, AST in 1.9 times, GGTP in 2.2 times, compared to normal (p < 0.05) in the absence of reliable changes in patients of the group II.

Simultaneously, in patients of group I with SIBO a significant decrease of nitrites concentration in the blood serum in 1.48 times was noticed on the background of increasing NO-synthase total activity in 1.6 times (p < 0.05), with concurrent trends to changes in these indicators in patients of group II.

Thus, the DE and SIBO combination in patients with DM type 2 leads to potentiation the violations of the functional liver state, atherogenic dyslipidemia and endothelial dysfunction.
Relationship between deviations in peripheral blood cell populations and selected clinical parameters in patients with primary biliary cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) constitutes an autoimmune liver disease characterized by progressive destruction of small- and medium-sized intrahepatic bile ducts. The role of Treg and Th17 cells in the course of PBC remains still uncertain. The aim of this study was to describe the percentages and absolute counts of Th17 and Treg cells in patients with newly diagnosed PBC and to assess the relationships between analyzed cell subsets and selected clinical parameters (pruritus and the degree of PBC severity).

Methods: The frequencies of Treg and Th17 cells were measured by flow cytometry in 40 previously untreated female patients with PBC. The control group consisted of 20 healthy age- and sex-matched volunteers. The diagnosis of PBC was based on the common known criteria. The degree of severity of PBC was evaluated in each patient by liver biopsy.

Results: Significantly lower frequencies and absolute counts of Treg cells were found in the study group in comparison to controls (p < 0.0001). Higher percentages and absolute counts of Th17 cells were found in the PBC patients in comparison to control group (p < 0.0001). The frequencies and absolute counts of Treg cells were higher in subjects with more advanced PBC. There was no such a relationship concerning frequencies and absolute counts of Th17 cells and histological stage of PBC. There were no statistical differences between the frequencies and absolute counts of both Treg and Th17 cells in patients with/without pruritus.

Discussion/Conclusion: Reduced number of Treg cells and higher level of Th17 cells could be responsible for the loss of immune tolerance and development of inflammatory and autoimmune process in PBC. In spite of Th17 cells, Treg cells correlate with histologic stage of PBC. Neither Th17 cells, nor Treg cells correlate with the presence of pruritus.
The regulatory properties of ions in the control of life cycle of hepatocytes

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The research on mechanisms of living system homeostasis control mechanisms identified patterns of strengthens the influence of substances with a reduction in their level of organization.

The aim of this study was to identify promising mechanisms of targeted control of hepatocytes lifecycle as a new method for the treatment of liver diseases.

Materials and Methods: The research was conducted in two stages. The first stage was provided with the use of knowledge from databases such as stitch.embl.de; proteinatlas.org; reactome.org and pantherdb.org to conduct estimation of hepatocyte-specific protein, their interaction and ways of identification of the most important ions. The second stage was carried out by modeling of control of hepatocytes lifecycle processes using a drug which are able to helm the flow of ions across the cytoplasmic membrane.

Results and Discussion: The study conducted using systems biology tools allowed identify a number of specific liver proteins, namely APOA2, A1BG, AHSG, F2, CFHR2, HPX, F9, CFHR2, SPP2, C9, MBL2, CYP2A6. In addition, there was formulated hypothesis regarding the selective sensitivity of hepatocytes to concentrations namely calcium, magnesium, sodium and potassium. In view of this fact conducted an experiment about the control of hepatocytes lifecycle through blocking or activation ion channels, showed that the addition of substances which blocks calcium channels after 24 hours of incubation results to a significant reduction of concentration of cells with apoptosis marks on the background of maintain the overall concentration.

Conclusions: The studies have shown the effectiveness of systems biology approaches to solving problems of the treatment of liver diseases. There was showed an efficiency of approaches to control intracellular calcium and potassium ions at certain stages of liver disease.
Survival of apoptosis-primed activated hepatic fibroblasts is Bcl-xL-dependent

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Introduction: Activated stromal fibroblasts (ASF) are the main stromal cell population in liver fibrosis and desmoplastic liver cancers and have been implicated in the development of these liver diseases. ASF display an activated phenotype and an increased sensitivity to apoptotic stimuli. This state of ‘apoptotic priming’ has been linked to changes in the cellular profile of apoptosis regulating Bcl-2 proteins. Targeting of Bcl-2 proteins in ASF could be explored for novel anti-fibrotic and anti-tumor therapies in the liver. Thus, our aim was to investigate the mechanisms of stromal cell activation with focus on regulation of pro- and anti-apoptotic Bcl-2 proteins involved in apoptotic priming.

Methods: For in vitro studies, human and mouse fibroblasts were either treated with platelet derived growth factor (PDGF) alone or in combination with small molecule inhibitors of the anti-apoptotic Bcl-2 proteins Mcl-1, Bcl-2 and Bcl-xL (BH3 mimetics). Fibroblasts were examined for Bcl-2 proteins and apoptosis by immunofluorescence microscopy, Western blot and qPCR. To investigate an anti-fibrotic potential of these compounds in vivo, the MDR2⁻/⁻ mouse model of liver fibrosis was employed. Mice were treated with BH3 mimetics and changes in liver histology, especially quantitative changes in fibrosis were assessed.

Results: In vitro treatment of fibroblasts with PDGF results in fibroblast activation, downregulation of Bcl-2 mRNA and upregulation of Bcl-xL protein. Addition of BH3 mimetics with selective specificity for Bcl-2 proteins reveals that survival of these activated cells is Bcl-xL dependent. In vivo studies demonstrate that pro-apoptotic BH3 mimetics reduce liver fibrosis in MDR2⁻/⁻ mice.

Discussion/Conclusion: PDGF induces apoptotic priming in fibroblasts is mediated by Bcl-2 protein alterations. Specific Bcl-xL inhibition results in selective apoptosis of ASF in vitro and reduction of liver fibrosis in vivo. Treatment of ASF with Bcl-xL inhibitors could represent a potential target for the therapy of liver fibrosis and desmoplastic liver cancers.
Correlation between Ulcerative Colitis Endoscopic Index of Severity, Lichtiger Index and fecal calprotectin in ulcerative colitis patients

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Introduction: Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory disease characterized by recurrent episodes of diffuse inflammation of the large intestine’s mucosa followed by periods of remission. In view of clinical management, it is essential to determine the disease activity. In order to evaluate it in a given patient, doctors rely on a combination of clinical and endoscopic findings as well as levels of laboratory biomarkers. Until now, there have been no prospective studies that have evaluated how endoscopic activity, assessed using UCEIS, correlates with clinical activity, evaluated using the Lichtiger Index, and with levels of fecal calprotectin (FCP) in UC. The purpose of our study was to answer the following question: what is the correlation between the UCEIS score, Lichtiger Index and the FC levels in UC patients.

Methods: This prospective study enrolled 58 patients – 32 male and 26 female at an average age of 39.4 ± 9 (18–63) years with UC, referred for colonoscopy to the Clinic of Gastroenterology of “Tsaritsa Yoanna” University Hospital in Sofia between May 2014 and April 2016. The diagnosis was made on the basis of standard clinical, endoscopic, and histologic criteria. UC patients (28 with active UC and 30 in remission) were scored clinically and endoscopically. Calprotectin was analyzed in stool samples by means of point-of-care desk-top Quantum Blue Reader® method.

Results: The UCEIS significantly correlated with levels of FCP (r = 0.869, p < 0.001) and the Lichtiger Clinical Activity Index (r = 0.862, p < 0.001). Moreover, the Lichtiger Index demonstrated significant correlation with FCP levels (r = 0.869, p < 0.001).

Discussion/Conclusion: The strong correlation with clinical and endoscopic disease activity suggests that FCP represents a useful biomarker for non-invasive monitoring of disease activity in UC patients.
NAFLD treatment – Difficulties and expectations

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Introduction: Treatment of NAFLD requires a consideration of which patients need to be treated, because not all patients progress to steatohepatitis, fibrosis or cirrhosis. Ursodeoxycholic acid (UDCA) is a secondary bile acid and its clinical properties include anti-apoptotic effects, decreasing endoplasmic reticulum stress and improving hepatic insulin sensitivity, suggesting that UDCA may be effective in the treatment of NAFLD. Pentoxifylline, a xantine derivate, seems to inhibit TNF-α. Aim of our study was to evaluate the role of UDCA and pentoxifylline in improvement of NAFLD evolution.

Methods: We included 50 patients with NAFLD evaluated by FibroMax at the beginning and in the end of the study, and excluded the patients with others conditions associated with hepatic steatosis. We divided the patients into two groups matched by gender, weight and fibrosis degree: group A (26 patients treated with UDCA 13 mg/kg/day) and group B (24 patients with UDCA 13 mg/kg/day plus 400 mg tid of pentoxifylline. All patients were also placed on a 1200-calorie diet but body mass index remained unchanged during the follow period-12 months and also the previous medication remained the same. In all patients we calculated BMI, WC, Fatty Liver Index (FLI), NAFLD Liver Fat Score (NAFLD-LFS) before medication and after 1 year. In both groups we determined aminotransferases, GGT, lipid profile, albumin, glucose, at the beginning and at the end of the study. No significant differences between the two groups in ALT, AST, GGT, and lipid profile at the beginning.

Results: After 1 year aminotransferases levels diminished in UDCA group compared with the initial values (without statistical significant from the beginning) and were normal in the combination group, with significant statistical difference between the start and the end of treatment (p < 0.001). FLI and NAFLD-LFS were significant better compared with the beginning in the second group but we also observed a better scores in UDCA group. No improvement for lipid profile in both groups. No differences during the study period in BMI, WC, presence of diabetes mellitus or metabolic syndrome in all patients. We noticed an improvement of fibrosis degree (evaluated by FibroMax) in the second group but without statistical significance compared with the start.

Discussion/Conclusion: UDCA in moderate dose improves aminotransferases levels and fatty liver scores in patients with NAFLD but the combination of UCDA with pentoxifylline seems to be more efficient in normalizing aminotransferases and also in fibrosis progress.
Outcomes from colonoscopic surveillance in patients with primary sclerosing cholangitis

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*Joint First Author

Introduction: Our hospital serves as a large tertiary referral centre for patients with inflammatory bowel disease. Current guidelines for patients with both inflammatory bowel disease and primary sclerosing cholangitis (PSC) recommend annual colonoscopy for dysplasia surveillance in this group of patients. We reviewed adherence to these guidelines, and outcomes of dysplasia surveillance colonoscopy.

Methods: Patient records between 2007 and 2013 were searched. Clinical records were reviewed to determine colonoscopy outcomes and reasons for no colonoscopy being performed. Patients with dysplasia found at surveillance colonoscopy were identified.

Results: 88 patients with PSC were identified from our records. 17 patients previously underwent colectomy for indications other than the presence of dysplasia at surveillance colonoscopy, most commonly for treatment-refractory colitis. 3 patients had relocated and 7 patients were deceased. 31 of the remaining 61 (51%) patients had undergone colonoscopy within the past year. 4 patients (6%) had dysplasia identified at surveillance colonoscopy.

Discussion/Conclusion: Uptake of colonoscopic surveillance needs to be improved. It is however possible that some patients have had endoscopies performed closer to home, but this was not documented. Patients with PSC may benefit from an annual checklist incorporated into an electronic patient record to ensure that cancer surveillance is appropriately performed.
How useful are colonoscopic surveillance protocols in patients with primary sclerosing cholangitis and colitis?

T. Partington*, J. Skinner*, A. Barnabas
St. Mark’s Hospital, London, UK
*Joint First Author

Introduction: Our hospital serves as a large tertiary referral centre for patients with inflammatory bowel disease. Current guidelines for patients with both inflammatory bowel disease and primary sclerosing cholangitis (PSC) recommend annual colonoscopy for dysplasia surveillance in this group of patients. We reviewed the clinical impact that these guidelines have, both in clinician and patient adherence to these guidelines, and prospective incidence of dysplasia.

Methods: Patient records between 2007 and 2013 were searched. Clinical records were reviewed to determine colonoscopy outcomes and reasons for no colonoscopy being performed. Patients with dysplasia found at surveillance colonoscopy were identified.

Results: 88 patients with PSC were identified from our records. 17 patients underwent colectomy for indications other than the presence of dysplasia at surveillance colonoscopy, most commonly for treatment-refractory colitis. 3 patients had relocated and 6 patients were deceased for reasons other than colorectal cancer. 31 of the remaining 61 (51%) patients had undergone colonoscopy within the past year. 5 patients (8%) had dysplasia identified at regular surveillance colonoscopy. 1 patient, who declined colectomy for low grade dysplasia, developed colorectal carcinoma.

Discussion/Conclusion: Surveillance guidelines are effective in this high risk group of patients. Uptake of colonoscopic surveillance needs to be improved. Patients with PSC may benefit from an annual checklist incorporated into an electronic patient record to ensure that cancer surveillance is appropriately performed.
Azathioprine drug management in patients with inflammatory bowel disease

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²Gastroenterohepatology Clinic, Skopje, Macedonia
³Institute of Physiology, Medical Faculty, Skopje, Macedonia

Introduction: Azathioprine (AZA) dosage is very important factor that has an impact on achieving remission and avoiding adverse effects (AE’s) as well in patients with inflammatory bowel disease (IBD). AZA intolerance is seen at lower starting dose, after which the drug is stopped or if there is a possibility the dose is decreased.

Methods: The aim of this study was to evaluate the relationship between the dose of AZA and the AE’s in patients with IBD. Two groups of patients were selected from the Gastroenterohepatology Department in Skopje. One group (39 patients) that was using AZA at the moment of this study and the other group (8 patients) had used AZA in the past and because of an AE’s the drug was stopped. Besides the routine hematological parameters, the concentration of alpha amylase was determined as well, and a correlation was done with the dose of AZA.

Results: The average value of AZA dose in patients that were using the drug at the moment of this study and had used it in the past was 164.7 mg ± 27.3 mg (min. 100 mg, max. 200 mg) vs. 50 mg ± 18.9 mg (min. 25 mg, max. 75 mg), respectively, p < 0.05. AE’s were analyzed in the group of patients that had used AZA at the moment of this study as well. The results have shown that the average value of AZA dose in patients where AE’s were observed was higher compared with the patients where no AE’s were seen (146.6 mg ± 30.4 mg vs. 168 mg ± 25.4 mg), p < 0.05. The average value of alpha amylase in patients treated with AZA at the moment of this study was 70.25 U/l ± 30.03 U/l. An increased dose of AZA correlated with increased values of alpha amylase in serum, p < 0.05.

Discussion/Conclusion: Most of the AE’s that can occur during the AZA treatment in patients with IBD are happening at lower dose of the drug. Increasing of AZA dose should be done step by step with careful monitoring of hematological parameters and hepatal enzymes.
Trends of serum IgG4 level testing in a UK tertiary hepatopancreatobiliary (HPB) centre and correlation with the diagnosis of IgG4-related disease (IgG4-RD)

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Introduction: IgG4-RD is an increasingly recognized disorder with significant implications if the diagnosis is not confirmed at an early stage. Population studies are limited but prevalence is estimated to be 0.8/100,000. This multi-system disease presents through multiple specialties and can mimic conditions such as primary sclerosing cholangitis, autoimmune liver disease, pancreatic cancer and retroperitoneal fibrosis. The Boston and HISORt criteria provide a recognized clinical, radiological, serological and histological framework for diagnosing IgG4-RD. Our tertiary HPB centre covers a population of 2.1 million in the South of England. IgG4-RD discussions are a major theme of our MDT. We aim to examine the trends of IgG4 testing and patient diagnoses within our network.

Methods: Immunopathology results databases were searched from 2009–2015 for the term “IgG4” (cut-off 1.3 g/l). Histological specimens were examined and confirmed using the standard Boston criteria. All patients identified fitted the HISORt inclusion criteria.

Results: 1137 adults were tested and 139 cases (12\%) had elevated IgG4 levels. The median age was 60 (range 18–97 years). Our testing has increased 4-fold and this trend is reflected in Graph 1 together with the number of cases diagnosed per year. The estimated prevalence was 0.62/100,000. Table 1 shows the origin of serum IgG4 requests within our network.

Discussion/Conclusion: Serum IgG4 is an important adjunct marker complimenting imaging, histology and clinical presentation for diagnosing IgG4-RD. The increasing number of serum testing has been paralleled by the number of cases diagnosed at our centre. However, our prevalence appears lower than expected and this might be explained by a genuine lack of cases or lack of recognition. The increasing number of IgG4 testing and associated costs supports the need for the development of diagnostic algorithms, guidelines and clinical models to develop integrated working between multiple stakeholders including HPB/liver units, primary and secondary care.
Table 1: Location/requests of serum IgG4 testing within our network

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of tests</th>
<th>Percentage of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&amp;E</td>
<td>8</td>
<td>0.61%</td>
</tr>
<tr>
<td>GP</td>
<td>323</td>
<td>24.59%</td>
</tr>
<tr>
<td>Respiratory Services</td>
<td>25</td>
<td>1.89%</td>
</tr>
<tr>
<td>Cardiac Services</td>
<td>1</td>
<td>0.08%</td>
</tr>
<tr>
<td>Mental Health Services</td>
<td>4</td>
<td>0.3%</td>
</tr>
<tr>
<td>Biochemistry/Hematology Lab</td>
<td>1</td>
<td>0.08%</td>
</tr>
<tr>
<td>Immunology Lab</td>
<td>10</td>
<td>0.8%</td>
</tr>
<tr>
<td>Endocrinology Services</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>80</td>
<td>6.1%</td>
</tr>
<tr>
<td>ENT</td>
<td>21</td>
<td>1.6%</td>
</tr>
<tr>
<td>Private Patients</td>
<td>18</td>
<td>1.4%</td>
</tr>
<tr>
<td>Vascular services</td>
<td>4</td>
<td>0.3%</td>
</tr>
<tr>
<td>Women’s Health services</td>
<td>5</td>
<td>0.4%</td>
</tr>
<tr>
<td>EAU/MAU/MAU</td>
<td>16</td>
<td>1.3%</td>
</tr>
<tr>
<td>Endoscopy Unit</td>
<td>1</td>
<td>0.08%</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>1</td>
<td>0.08%</td>
</tr>
<tr>
<td>Haematology Ward</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>General Surgeons</td>
<td>25</td>
<td>1.9%</td>
</tr>
<tr>
<td>Gastroenterology Services</td>
<td>17</td>
<td>1.3%</td>
</tr>
<tr>
<td>Stroke Unit</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>GUM services</td>
<td>1</td>
<td>0.08%</td>
</tr>
<tr>
<td>ITU/HCU</td>
<td>9</td>
<td>0.7%</td>
</tr>
<tr>
<td>Renal Unit</td>
<td>2</td>
<td>0.15%</td>
</tr>
<tr>
<td>Rheumatology services</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>SSU/SAU/DSU</td>
<td>10</td>
<td>0.8%</td>
</tr>
<tr>
<td>Dermatology</td>
<td>1</td>
<td>0.08%</td>
</tr>
<tr>
<td>Outpatients, mixed gastroenterology, hepatology and HPS clinic</td>
<td>559</td>
<td>42.6%</td>
</tr>
<tr>
<td>Other</td>
<td>159</td>
<td>12.09%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1313</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>
Experience of IgG4-related disease (IgG4-RD) in the UK: An online national survey

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Introduction: IgG4-RD is an increasingly recognized disorder. Population studies are limited but prevalence is estimated to be 0.8/100,000. This multisystem disease presents through multiple specialties and can mimic conditions such as pancreatic cancer. The HISORt criteria provide a recognized clinical, radiological serological and histological framework for diagnosing IgG4-RD. Our tertiary hepatopancreatobiliary (HPB) centre covers a population of 2.1 million in the South of England. Our aim was to understand current knowledge around IgG4-RD nationally.

Methods: A ten-question web-based survey around IgG4-RD was distributed to members of the British Society of Gastroenterology.

Results: Our national survey had 63 responses from consultants (68%), trainees (28%) and others. All were aware of IgG4-RD. 68% felt confident in diagnosing and 62% in treating the condition. 55% of respondents checking IgG4 serum levels in patients with cholangiopathy, 44% in retroperitoneal fibrosis and 25% for pancreatic lesions or pancreatitis. 25% of responders were aware of the diagnostic criteria but 62% had not heard of them. Half of the respondents had seen 1–3 cases of IgG4-RD with 10% having not seen a case personally. 8% of respondents had either no IgG4-RD service or did not know who ran it. One centre has a monthly MDT. All trainees reported poor training and awareness around the condition.

Discussion/Conclusion: Although this survey had only a relatively small number of respondents, there was representation across the UK. In our experience there is heterogeneous clinical practice around IgG4-RD across the UK. It appears that the lack of coordinated efforts and possibly the lack of education and awareness may be preventing the development of local services. We advocate and support the establishment of guidelines, regional units/networks, teaching curricula and formal referral pathways as well as collaborations with tertiary HPB/Liver centres for the early and appropriate management of IgG4-RD in the UK.
Molecular therapy targeting vascular endothelial growth factor is not equally effective in all HCC types

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Introduction: The use of molecular targeted therapy for hepatocellular carcinoma (HCC) continues to expand. Existing database shows that inhibition of vascular endothelial growth factor (VEGF) signaling may affect tumor growth through several mechanisms. Sorafenib inhibits several tyrosine kinase receptors, including VEGF receptor (R)-2 and 3, PDGFR-β, FLT-3 and C-kit. However, clinical studies involving patients with HCC present various and often disappointing results. We hypothesized that VEGF inhibiting may not be equally effective due to different HCC types.

Methods: Study performed experimentally as number of patients is limited and research design require various types of HCC. Human HCC cells lines Hep3B, HepG2, and Sk-hep-1 were cultivated in modified media seeded onto well plates. VEGF-targeting drug sorafenib 0.05 mg/ml added in cultures. General cells count and nuclei morphology were visualized with the TUNEL-staining protocol and cells viewed with a fluorescence microscope (magn. x400). The number of apoptotic cells calculated in percentage of total nuclei. Apoptosis related cytokines were analyzed by Western blotting.

Results: VEGF inhibition-associated changes become evident in HepG2/Hep3B cell lines after 48 hours of treatment leading to a significant time-dependent reduction of cell numbers of 67.9–83.2% (p < 0.01). Cells became sparse, rounded, and detached from the dishes representing morphologic signs of apoptosis. This correlated with statistically significant activation of caspase-9, caspase-3, and caspase-6 (0.001 < p < 0.05). However, Sk-hep-1 cell culture responded much worse with only 36.7–43.7% reduction during same time interval.

Discussion/Conclusion: Present study shows that VEGF-targeted therapy may act through parallel mechanisms that have more or less important role depending on tumor type. In certain malignancies VEGF-targeted therapy may have significant activity, whereas in other has no clinical benefit. Our study gives one of the possible explanations to the fact of variations in clinical response rate of VEGF-targeted therapy, e.g. different subtypes of HCC have different sensitivity to VEGF-targeted therapy.
Calprotectin in the ulcerative colitis diagnosis in patients with autoimmune hepatic disorders

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²Rostov State Medical University, Rostov-on-Don, Russia

Introduction: The incidence of extraenteric manifestations of inflammatory bowel disease (IBD) and association of IBD with autoimmune hepatic disorder imply the need for thorough examination of the patients in order to exclude these organs involvement which tends to have long-term latent course and a number of serious complications.

The research objective: To evaluate the efficacy of calprotectin (FC) detection as a target screening marker of ulcerative colitis (UC) in patients with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Methods: 15 autoimmune hepatic disorders (AHD) patients have been examined: 12 had PBC, 3 had PSC (mean age 45 ± 6; 13 women, 2 men). AHD diagnosis was verified by clinical-laboratory and immunological investigations, paracentetic liver biopsy, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiography.

Results: The range of clinical symptoms in AHD patients is represented by meteorism, flatulence, unstable stool with diarrhea episodes without blood and mucus. FC was determined in all patients, (mean value 156.6 mg/g; FC range 42–400 mg/g). In 11 cases (73.3%) total ileocolonoscopy and morphological investigation of large intestine mucous membrane revealed markers of active UC. The FC level depended on UC prevalence. In 3 large intestine total lesion cases (1 case with PSC and UC, 2 cases with PBC and UC), 27.3%, mean FC value was 394 mg/g. In 4 left-side UC localization cases (2 cases with PSC and UC, 2 cases with PBC and UC), 36.4%, mean FC value was 298 mg/g. In distal UC (1 case with PBC and UC) FC concentration was 136 mg/g.

Conclusions: The examined AHD patients group revealed increased calprotectin level in 53% of cases. AHD diagnostic algorithm should include calprotectin detection as UC diagnosis screening method.
Effect of *Helicobacter pylori* eradication on hepatic steatosis, NAFLD fibrosis score and HSENSI in non-alcoholic steatohepatitis patients: A MRI-based pilot open-label study

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**Introduction**: Limited clinical data suggest that *Helicobacter pylori* (Hp) infection may contribute to the pathogenesis of non-alcoholic fatty liver disease (NAFLD). The aim of this study was to evaluate the effect of Hp eradication on hepatic steatosis (magnetic resonance imaging [MRI]), NAFLD fibrosis score and HSENSI (Homocysteine, serum glutamic oxaloacetic transaminase [SGOT], Erythrocyte sedimentation rate [ESR], Nonalcoholic Steatohepatitis [NASH] Index) in NASH patients.

**Methods**: Thirteen adult patients with biopsy-proven NASH, asymptomatic for gastrointestinal disease, underwent ¹³C-urea breath test; Hp-positive patients received eradication therapy until repeat test became negative. Hepatic fat fraction (HFF), standard biochemical tests and calculation of NAFLD fibrosis score and HSENSI were performed at baseline and month 12.

**Results**: HFF was similar for between and within group comparisons. NAFLD fibrosis score showed a non-significant trend towards decrease in Hp(+) (-0.34 [-1.39–0.29] at baseline and -0.24 [-0.99–0.71] at month 12; p = 0.116), whereas increase in Hp(-) group (-0.38 [-1.72–0.11] and -0.56 [-1.43–0.46], respectively; p = 0.249). HSENSI was significantly decreased only in Hp(+) group (1.0 [1.0–2.0] at baseline and 1.0 [0–1.0] at month 12; p = 0.048).

**Discussion/Conclusion**: Hp eradication treatment had no long-term effect on hepatic steatosis assessed by MRI, but showed a trend towards improvement in NAFLD fibrosis score and HSENSI, which are also noninvasive indices of hepatic fibrosis and NASH, respectively. Although these results should be interpreted with caution, mainly because of the small sample size of this pilot study, larger studies with repeat paired biopsies are warranted.
Decreased fibrogenesis in CH25H⁻/⁻ mice in a mouse model of intestinal fibrosis

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Introduction: Crohn’s disease (CD) is a chronic immune-mediated inflammatory condition of the gastrointestinal tract. Intestinal stenosis and fibrosis are common complications of CD. Oxysterols are oxidized derivatives of cholesterol and have recently been recognized as immune-modulators and chemoattractants. Cholesterol 25-hydroxylase (CH25H) mediates enzymatic conversion of cholesterol to 25-hydroxycholesterol (25-HC), which was shown to modulate immune responses and oxidative stress. In vitro analysis of human fetal lung fibroblasts demonstrated 25-HC to be able to promote alpha-smooth muscle antigen expression and collagen production, augment the release of matrix metalloproteinase 2 and 9 and stimulate transforming growth factor-beta release. We are aiming to characterize the role of CH25H in the development of intestinal fibrosis.

Methods: Small bowel resections from donor mice, either wildtype or CH25H knockout littermate mice, were transplanted subcutaneously into the neck of a recipient mouse of the same genotype. 7 days after surgery the intestinal grafts were isolated and examined for collagen layer thickness and mRNA expression of fibrosis mediators.

Results: In our in vivo fibrosis model, mice deficient for the CH25H enzyme developed a significantly thinner collagen layer compared to wildtype littermates (10.73 ± 1.37 vs. 14.22 ± 1.26 µm, respectively). Reduced collagen deposition in CH25H⁻/⁻ animals was confirmed by automated microscopy quantification of total collagen content. mRNA expression of fibrosis mediators including lysyl oxidase-like 2, collagen type 1 and type 3 was decreased in CH25H⁻/⁻ mice compared to wildtype littermates as confirmed by qPCR.

Discussion/Conclusion: Our findings suggest an involvement of CH25H in the development of intestinal fibrosis. CH25H deficiency partially prevented development of fibrosis, pointing to oxysterols as a potential new treatment option for CD associated fibrosis. Further mechanistic and therapeutic studies will be necessary to develop this option.
Systematic review of the clinical disease severity indices for inflammatory bowel disease

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Introduction: Clinical disease severity indices are increasingly being used in choosing treatment and monitoring response of patients with inflammatory bowel disease (IBD). Our aim is to systematically review the clinical disease severity indices in IBD and to appraise their measurement properties and methodological quality.

Methods: We searched the PubMed, Embase and PsycINFO databases for original articles describing the development and/or evaluation of one or more of the measurement properties of clinical disease severity used in IBD. We assessed these properties (e.g., internal consistency, reliability, validity, responsiveness) using a standardized checklist.

Results: We examined the full text of 142 articles that we deemed potentially eligible and identified 22 clinical disease severity indices in IBD. No clinical disease index has met all the required measurement properties. All of the validation studies were not descriptive enough to allow assessment of their methodology.

Discussion/Conclusion: Although commonly used in multiple clinical trials, none of the clinical disease severity indices in IBD had all the required measurement properties. Further validation studies are required.
Involvement of cytokines of IL-20 subfamily in the pathogenesis of coeliac disease

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Introduction: Cytokines of interleukin (IL)-20 subfamily, IL-19, IL-20 and IL-24 were suggested to be involved in immunoregulation and tissue remodelling, however their role in the pathogenesis of coeliac disease (CD) is completely unknown.

Methods: Expression of IL-19, -20, -24 and their common IL-20RB receptor was investigated by real-time PCR in the duodenal biopsy samples of children with CD and controls. Localization of IL-24 and IL-20RB was determined by immunofluorescence staining. Effect of different stimulatory factors (IL-1β, IL-17, TGF-β, TNF-α, LPS) was investigated on the mRNA expression of IL-19, -20, -24 and -20RB of peripheral blood mononuclear cells (PBMC), duodenal epithelial and fibroblast cells. To determine the effect of IL-24 on duodenal epithelial cells next-generation sequencing analysis was performed.

Results: We found elevated IL-19 and IL-24 expression in the duodenal mucosa of children with CD compared to controls. IL-1β increased the mRNA expression of IL-19, -20, -24 and -20RB and also the IL-24 protein production of PBMC, epithelial and fibroblast cells. IL-24 decreased the expression of apoptosis-related genes in duodenal epithelial cells.

Discussion/Conclusion: Increased presence of IL-20 subfamily members in the duodenal mucosa of children with CD suggests their role in disease pathogenesis. Based on our in vitro results we suggest that IL-20 subfamily of cytokines has a potential role in the maintenance of mucosal integrity.

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Hypoxia inhibits intestinal inflammation through the activation of autophagy and the suppression of NLRP3

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Introduction: The impact of environmental hypoxia on inflammatory bowel disease (IBD) is controversial, with studies supporting both a pro-inflammatory and a protective effect. Hypoxia regulates autophagy and inflammasome pathways, two innate immune mechanisms linked by mutual regulation that are implicated in IBD. Evidential data suggest that the imbalance in the mutual regulation of autophagy and pyrin domain containing (NLRP)3 inflammasome under hypoxia plays a role in the development of IBD.

Methods: Healthy volunteers (n = 10), patients with Crohn’s disease (CD, n = 11) and patients with ulcerative colitis (n = 9) were subjected to hypoxic conditions resembling an altitude of 4000 m above sea level for 3 h using a hypobaric chamber. Wild-type, interleukin (IL)-10-/-, Nlrp3-/- and IL-10-/- Nlrp3-/- double knockout mice were subjected to hypoxia (8% O2) for 18 h prior to colon biopsy collection. The human monocytic cell line THP1 and the intestinal epithelial cell line HT-29 were subjected to hypoxia (0.2% O2) in the presence and absence of lipopolysaccharide.

Results: Hypoxia inhibited tumor necrosis factor (TNF)α and NLRP3 mRNA expression concomitantly with the induction of the autophagy-associated gene p62 in colon biopsies of patients with CD. In normoxia, IL-10-/-, but not IL-10-/- Nlrp3-/- mice presented increased NF-κB activation and mRNA expression of TNFα, IL-6, and inflammasome-associated IL-1β concomitantly with an accumulation of autophagy proteins. Hypoxia inhibited inflammation and restored autophagy in IL-10-/- mice. In THP1 and HT-29 cells, hypoxia inhibited NF-κB activation concomitantly with an increase in autophagy and the repression of the autophagy inhibitor mTOR. siRNA-mediated silencing of NLRP3 further activated autophagy under hypoxia.

Discussion/Conclusion: Our results suggest a protective effect of hypoxia in CD patients and IL-10-/- mice. Moreover, this study confirms a reciprocal regulation between hypoxia, inflammation and autophagy, and suggest that hypoxia ameliorates inflammation through the induction of autophagy via the regulation of NLRP3.
Differences in sequences between HBV relaxed circular (RCDNA) and covalently closed circular DNA (cccDNA) forms

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Introduction: The HBV genome exists in two different forms: cccDNA and RCDNA. There are some reports that free cccDNA 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). Another goal of this study was to compare polymorphisms in cccDNA and RCDNA forms.

Methods: Serum and liver biopsy samples were collected from 67 CHB patients at the same time point. Genotyping of RCDNA form was done directly after DNA extraction. For the cccDNA analysis samples were treated with the T5 Exonuclease which degrades ssDNA and linear or circular dsDNA with gaps and nicks. cccDNA was present in all liver samples and in none serum sample. Next, the mass spectrometry analysis was performed to compare RC and cccDNA sequence. HBV mutations associated with drug resistance located in the HBV pol (P) region and mutations located in the HBV basal core promoter/pre-core region (BPC/PC) were included.

Results: The BPC/PC and P sequence of RCDNA extracted from liver and blood samples were different in 38% and 11% of patients, respectively. Differences were also found between RC and cccDNA extracted from the same liver specimen. 60% of these samples have differed in the BPC/PC region and 40% in the P region. The most frequently found differences were at codon 1764, 1899 and 1762. The BCP/PC mutations were associated with HBeAg negativity and lower viral load.

Discussion/Conclusion: We have demonstrated that there are differences in the sequence of RCDNA and cccDNA extracted from the same liver specimen. However, further investigations are needed to analyze if mutations in cccDNA are conserved and whether cccDNA serves as a ‘mutation storage’ pool for HBV. This could have profound implications for subsequent therapy choice for the treatment-experienced patients.
“I can’t give IV fluids, they’ve got ascites!”: Improving the management of patients with acute decompensated chronic liver disease at a regional hospital in the United Kingdom

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Introduction: Patients with acute decompensated chronic liver disease (AD-CLD) are complex to manage, especially for non-specialists. The prevalence of CLD is rising in the United Kingdom (UK) but mortality rates continue to worsen. The 2013 National Confidential Enquiry in to Patient Outcomes and Deaths (NCEPOD) report “Measuring the Units” concluded, in part, that suboptimal initial medical care of patients with AD-CLD was a cause for this. The British Society of Gastroenterology therefore created the “Decompensated Cirrhosis Care Bundle – First 24 Hours,” a checklist that guides the user through a ‘gold standard’ of clinical investigation, intervention and treatment. We aimed to improve the quality of care of these patients at our regional hospital in the UK.

Methods: From September 2015, we conducted focussed junior doctor teaching and introduced the bundle to routine practice. Clinical outcome data for all patients admitted with AD-CLD from March to September 2015 were collected retrospectively (‘pre-intervention’) using hospital notes and electronic patient records. This included completion levels of appropriate investigations and treatment strategies, as defined by the bundle, lengths of stay and readmission rates. From September 2015 to March 2016, data was recorded prospectively (‘post-intervention’).

Results: There were 33 admissions (12 individual patients) pre-intervention and 30 (22 individuals) after. Performance in all aspects improved. For example, ascitic tap was conducted in 71% of patients with ascites before versus 91% after, blood culture testing increased from 15% to 73% and abdominal ultrasound from 33% to 97%. Mean length of stay was similar (6.4 days vs. 7.6 days) but readmissions decreased. Pre-intervention, readmissions totalled 16 extra patient-days and 4 patients were not readmitted. Post-intervention, there were 6 additional patient-days, with 11 patients not readmitted.

Discussion/Conclusion: Targeted education and use of an intuitive care bundle can improve non-specialists’ care of patients with AD-CLD. It can also reduce readmission rates, likely at significant overall cost saving.
An audit of ERCP in a district general hospital

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Introduction: The audit was undertaken to provide accurate success and complication rates to patients undergoing ERCP.

Methods: Consecutive procedures from a single ERCP endoscopist's practice were included. Data on indications, results and early complications were collected prospectively.

Results: 101 procedures from a 6 months period were studied. In 73 (73%) the ampulla was intact (no earlier sphincterotomy). The majority of cases (65%) were undertaken for gallstone disease, 22% for suspected cancer, 3% stent occlusion, and 10% for other causes. In 3 cases cholangiography showed no pathology but in each there had been concern of choledocholithiasis. MRCP was carried out on 48 cases. In 71% of the cases the ERCP was primarily therapeutic.

In 35% of the cases biliary cannulation failed. Procedure was abandoned in 24 cases (because of the pathology encountered, unable to cannulate the papilla, patient discomfort, unable to cannulate CBD or because of full stomach).

There were no deaths during the immediate post-operative period. Complications occurred in 19 (19%) of procedures. The commonest complication was acute pancreatitis. It occurred in 10 (5.0%) cases of which 9 were mild and quickly self-limiting. In the other, respiratory failure responded to conservative measures. No surgical or radiological intervention was required. There were no other complications such as bleeding, perforation or infection.

Discussion/Conclusion: ERCP can be practiced successfully in a DGH setting but complication rates are not insignificant.
Initial management of acute upper gastrointestinal haemorrhage in a district general hospital

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Introduction: Acute upper gastrointestinal bleeding is the commonest emergency managed by gastroenterologists. Mortality is reported to be lower in specialist units and this is probably because of adherence to protocols and guidelines. The aim of this audit was to look into the compliance with the National Guidelines.

Methods: Information was gathered retrospectively on 50 patients admitted to a district general hospital with acute upper gastrointestinal haemorrhage. They were 16 females and 34 males with age range of 18–90 years.

Results: Results showed that 92% of the patients were admitted under non gastroenterologist physician as part of the on call take. Majority of patients (90%) was referred to the gastroenterologist within the first 24 hours of admission. The severity of the bleeding was assessed in only 44% of the patients using Rockall scoring system. The circulatory volume was restored in all of the patients with intravenous fluids or blood transfusion. Not all of the patients (only 44%) had an endoscopy within 24 hours and there was no out of hours endoscopists on site unless the on call physician was a gastroenterologist.

Discussion/Conclusion: The initial management of acute upper gastrointestinal bleeding is very important. In a district general hospital, the lack of out of hour endoscopists and the long waiting time for the endoscopy list may delay the appropriate timing of endoscopy. Our study showed that we need to train junior doctors how to use the Rockall scoring system. Following this audit, a standard Performa for clerking patients with upper gastrointestinal bleeding was developed.
Urgent referrals for upper GI endoscopy: District general hospital experience

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Introduction: Unfortunately, most cancers of the upper gastrointestinal (GI) tract are not diagnosed at an early stage. Therefore, it is important for GP’s to refer patients with suspected symptoms as early as possible. The appropriateness of the indications for OGD is crucial in referring patients to endoscopy units, improving cost-effectiveness and providing better patient care. The aim of this study was to evaluate the appropriateness of urgent referrals to the endoscopy unit to reduce unnecessary referrals.

Methods: Over a four month period, information was gathered retrospectively on 90 patients referred to the Endoscopy Units for urgent oesophagastroduodenoscopy (OGD). The appropriateness of referrals was established using NICE clinical guidelines, and Welsh cancer standards referrals standards.

Results: The results showed that 24% of patients referred for urgent OGD did not meet the referral criteria. Out of those inappropriate referrals, only 2 referral was downgraded by the consultant. Of those who met the criteria, 93% of patients were not seen within 7 days which is recommended by the guidelines and 8% of them waited longer than 28 days to be seen after being referred. Four patients (4.4%) referred were diagnosed with adenocarcinoma of the oesophagus and two patient (2.2%) were diagnosed with Barrett’s oesophagus. The rest had other non-malignant conditions.

Discussion/Conclusion: The use of the national guidelines to make appropriate referrals for the endoscopy unit can improve patients’ selection for the procedure. However, to avoid missed diagnoses of serious disease, using the guidelines must be tailored to the specific clinical setting.
Treatment efficiency and copper metabolism marker evaluation in Wilson’s disease patients during pathogenic therapy

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Introduction: Wilson’s disease (WD) is a severe genetic disturbance. Early starting adequate copper elimination therapy effectively prevents liver damage progression or limits disease severity, improves life prognosis.

Methods: Copper metabolism markers and treatment efficiency were analyzed in 87 WD patients receiving pathogenic treatment for at least 1 month. Therapy was carried out with penicillamine (PA) in 65 patients (33 males, 32 females, aged 3–63 years [Me = 34]), zinc sulfate (ZnS) in 9 (7 males, 2 females, aged 15–50 years [Me = 37]) and their combination in 13 patients (6 males, 7 females, aged 20–48 years [Me = 25]). Median starting doses were: PA – 750 mg/day, ZnS – 450 mg/day, and in combination: PA – 750 mg/day and ZnS – 375 mg/day. Treatment efficiency target levels were daily urinal copper excretion (DUCE) – below 0.5 and 0.075 mg during PA and ZnS treatment, respectively, and serum free copper (SFC) concentration below 0.25 mg/l.

Results: During PA treatment target levels of DUCE were achieved in 25 (39%) patients, of SFC – in 35 (54%), lack of effect – in 2 (3%), and 17 (26%) developed copper metabolism markers deterioration. During ZnS treatment target levels of DUCE were achieved in 3 of 9 patients, of SFC – in 7. During combined treatment target levels of DUCE were achieved in 10 of 13 patients, of SFC – in 2, lack of effect – in 1.

Discussion/Conclusion: PA and ZnS therapy is relatively efficient in WD patients, nevertheless, copper metabolism markers deterioration in 26% of patients during PA treatment requires careful dose choice and copper metabolism markers deterioration causes analysis.
How does the non-alcoholic steatohepatitis influence the course of ischemic heart disease?

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The presence of the lipid metabolism disorders, obesity can be regarded as factors of early development and progression of the ischemic heart disease (IHD) in patients of working age. Metabolic changes lead to violations of the liver function, non-alcoholic steatohepatitis (NASH) development, which potentiates the formation of atherogenic dyslipidemia with increased possibility of acute cardiovascular events.

The aim – to study the lipid changes character in patients with IHD considering the concomitant NASH presence.

Materials and Methods: The study involved 74 patients with IHD (stenocardia II, III functional class), aged 30–79 years, including 21 (28.4%) women, 53 (71.6%) men. The duration of IHD was 2–10 years. The coexistent NASH was found in 25 (33.8%) patients, the duration of NAFLD was 3–7 years. The viral and alcoholic etiology of liver injury was excluded. Patients didn’t take statins. Depending on the NASH presence patients were divided into 2 groups: I (n = 25) – IHD patients with the concomitant NASH; II (n = 49) – IHD patients without NASH. The blood lipids were assessed: total cholesterol, triglycerides (TG), HDL-C, LDL-C, atherogenic index (AI); the liver functional state indicators in serum: alanine (ALT), aspartic (AST) aminotransferases, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin.

Results: The average age of group I patients with concomitant NASH was 44.85 ± 7.2 years, all the patients were younger than 60 years. The average age of group II patients was 59.85 ± 8.9 years, 27 (55.1%) patients were older than 60 years. The presence of myocardial infarction (MI) in anamnesis was found in 14 (56%) patients of group I with concomitant NASH and in 4 (8.16%) patients of group II. In the group I it was registered the increased activity of ALT up to 67.19 ± 22.4 U/l, AST – up to 45.09 ± 19.7 U/l, GGT – up to 76.41 ± 23.6 U/l; ALP and total bilirubin indicators were within normal ranges. In the group II all functional liver indexes did not differ from the norm. In the group I the increased levels of cholesterol in 21 (84%), TG – 17 (68%) patients were found: 6.31 ± 1.42 mmol/l and 2.69 ± 1.23 mmol/l, respectively, AI was 5.04 ± 1.49. In the group II the increased concentration of cholesterol was noted in 26 (53.06%), TG – in 19 (38.77%) patients: 5.09 ± 1.17 mmol/l and 1.86 ± 1.08 mmol/l, respectively, AI was 4.16. Indicators of HDL-C, LDL-C did not differ between groups.

Thus, in patients with ischemic heart disease and concomitant NASH more pronounced dyslipidemic violations were found, that were accompanied with the rising incidence of MI in people of the working age.
Role of lactase deficiency in forming of dyspeptic syndrome in patients with irritable bowel syndrome associated with small intestine bacterial overgrowth

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While choosing tactic of patients’ management with irritable bowel syndrome (IBS), it is necessary to consider that motor-evacuating function of intestine leads to development of the syndrome of intestine bacterial overgrowth (SIBO), indigestion. Symptoms of milk intolerance can be connected with forming of secondary lactase deficiency (LD) which needs additional research.

The aim – to estimate the role of LD in development of dyspeptic syndrome in patients with IBS associated with SIBO.

Materials and Methods: 41 patients with IBS associated with SIBO were observed, including 29 (70.7%) males, 12 (29.3%) females. All patients had dyspeptic symptoms (abdominal pain or discomfort, diarrhea, constipation, bloating, nausea, vomiting) that increased in 20–60 minutes after consumption of milk with 3.2–3.5% fat content in dose of 250 ml or other containing lactose products. We measured height and weight of patients, determined their body mass index (BMI). Hydrogen breath tests (HBT) with lactose and lactulose were conducted to diagnose SIBO and its combination with LD.

Results: According to the results of HBT with lactose and lactulose, isolated SIBO was determined in 25 (60.9%), SIBO associated with LD – in 16 (39%) patients. An average age of patients with isolated SIBO was 26 ± 7.8 years, but in condition of SIBO and LD association – 54 ± 4 years. In the group with isolated SIBO patients’ weight was 64.2 ± 7.1 kg, height – 172.6 ± 8.6 cm, BMI – 21.5 ± 2.3 kg/m², and in group with connected SIBO with LD weight was 73.5 ± 4.5 kg, height – 175.9 ± 6.8 cm, BMI 23.6 ± 1.9 kg/m². In conditions of isolated SIBO abdominal pain was occurred in 20 (80%) patients, diarrhea – in 14 (56%), constipation – in 11 (44%), bloating – in 19 (76%) patients. When association of SIBO and LD had a place, abdominal pain disturbed 11 (68.8%) patients, diarrhea – 16 (100%), bloating – 12 (75%) patients, constipation was not noticed. Symptoms of milk intolerance disturbed patients with SIBO for 5.3 ± 3.4 years, and in condition of SIBO and LD association – 7.5 ± 3.6 years.

Conclusions: In patients with IBS associated with SIBO, dyspeptic syndrome can be accompanied by symptoms of milk intolerance without LD in 60.9% cases. Combination of SIBO and LD is noticed among patients of elder age group with higher duration of IBS, which can be an evidence of intestine mucus membrane affection with functional disorder of enterocytes.
The use of 5-aminosalicylic acid in children and adolescents with inflammatory bowel disease in Switzerland

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Introduction: Guidelines for the treatment of paediatric inflammatory bowel disease (IBD) include local and systemic therapeutic options. In ulcerative colitis (UC) 5-aminosalicylic acid (5-ASA) is recommended as primary therapy for mild-to-moderate disease; furthermore there is strong evidence demonstrating the benefits of topical 5-ASA in distal disease and in combination therapy for extensive disease. In Crohn’s disease (CD) the evidence for a beneficial role of 5-ASA is weak.

Methods: Data of patients < 18 years, registered between April 2008 and December 2015 in the Swiss Inflammatory Bowel Disease Cohort, were analysed.

Results: 320 paediatric IBD patients were included; 189 with CD and 131 with UC. Most UC patients presented with extensive colitis or pancolitis (88 [70%]) and only 24 (19%) with left-sided colitis or proctitis (13 [11%]). More than one third of UC patients (51 [39%]) received topical 5-ASA therapy and 43 (33%) combination therapy during their disease course. UC patients with left-sided colitis were more likely to receive topical or combination therapy as compared to patients with pancolitis (p < 0.001 and p = 0.001, respectively). An increase in the use of topical 5-ASA therapy in UC patients was noted over time. According to Paris classification most CD patient had ileo-colonic disease (L1 (ileal) 24 [13%], L2 (colonic) 24 [13%], L3 (ileo-colonic) 127 [71%]). Forty-seven percent of CD patients were treated with oral 5-ASA during their disease course. The usage was stable over time at around 15–20%.

Discussion/Conclusion: In recent years a very positive trend showing an increase in topical 5-ASA therapy in children and adolescents with UC has been demonstrated. However topical therapy is still underused, especially in patients with a more extensive disease. Conversely, despite weak evidence supporting 5-ASA use in CD patients it was frequently prescribed. Physicians should continue to encourage their UC patients to use topical therapy.
Whether elevated urea creates risk for NAFLD?

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Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is a condition of the liver that is characterized by fat accumulation in the liver, occurring in individuals who do not consume alcohol. Activation of renin-angiotensin-aldosterone system (RAAS) has been proved in patients with NAFLD. Blood urea nitrogen (BUN) elevation is a high risk factor and biomarker of RAAS activation of heart failure and coronary heart disease. We aimed to explore the relationship between BUN levels and metabolic changes in patients with fatty liver disease.

Materials and Methods: 115 male patients with biopsy proven fatty liver disease and 45 healthy controls with normal renal and hepatic function who are involved in the study. BUN levels were reviewed retrospectively. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were employed to estimate inflammation. We analyzed the correlation between BUN and fatty deposition or inflammation. Non-alcoholic fatty liver disease can be separated into two main categories: Simple steatosis: The presence of fat in the liver without much inflammation or fibrosis. Non-alcoholic steatohepatitis (NASH): Fat along with inflammation and varying amounts of fibrosis.

Results: The mean BUN levels of patients and controls were 4.89 (4.04–5.5) and 4.75 (3.92–5.67) mmol/l. Patients were grouped as simple steatosis (n = 48, 41.74%), and nonalcoholic steatohepatitis (n = 67, 58.26%). BUN levels of histologic subgroups were 4.69 ± 1.03, 5.12 ± 1.09 and 4.69 ± 1.15 mmol/l. In our study, we couldn’t find any differences between the patient groups and control group in relation to BUN levels.

Conclusion: We have not shown that patients with fatty liver disease have a higher BUN. Our findings that patients with NAFLD wasn’t any relationship between BUN levels and metabolic changes.

Key words: Non-alcoholic fatty liver disease, blood urea nitrogen
Introduction: Possible genetic predisposition to IBD is extensively discussed. Although the complex interaction among genetics have been long recognized among researchers, the understanding of its contribution to IBD pathogenesis continues to evolve. Genetic factors not only determine personal predisposition to particular pathogenetic mechanism, but also may potentially predict therapeutic response and treatment efficacy. About 30 genes are known to play role in IBD etiology and their number is expanding. We hypothesized that C-590T polymorphism of IL-4 gene and 35DelG polymorphism of Gap junction β2 protein/connexin (GJB2) gene (suspected to be responsible for Ludwig van Beethoven’s IBD and deafness) may have pathogenetic role in IBD.

Methods: Totally 102 (UC, CD) patients participated in the study. Diagnosis and management provided according to ECCO Guidelines. Female – 31 (30.4%), male – 71 (69.6%), control group – 40 practically healthy individuals (female – 17 [42.5%], χ² = 1.88, p > 0.05, male – 23 (57.5%), χ² = 1.38, p > 0.05). Cytokines determined in ELISA. Level of cytokines’ production statistically calculated according to control group quartiles. ‘Low’ (LQ) was IL1β < 23 pg/ml (lower quartile of control), TNFα ≤ 15 pg/ml, IL4 ≤ 4.95 pg/ml, IL10 ≤ 15 pg/ml and IL13 ≤ 28 pg/ml, respectively. ‘High’ (HQ) was TNFα > 32 pg/ml (upper quartile), IL1β ≥ 60 pg/ml, IL4 ≥ 45 pg/ml, IL10 and IL13 ≥ 25.96 pg/ml and ≥ 38 pg/ml, respectively. Frequencies of GJB2 (rs80338939) and IL-4 (rs2243250) mutations were analyzed in PCR.

Results: Homozygous GJB2 gene mutation (35DelG) in control has frequency of 5.0%, whereas among IBD patients – in every second person, by 20.58% more often in male, χ² = 38.32, p < 0.001. The distribution of IL4 (C590T) genotypes between groups including stratification upon gender was similar. The presence of GJB2 mutation in haplotype, regardless of IL4 (C590T) genotypes, increases the likelihood of IBD (UC, CD) 7.5 and 15.0 fold (OR = 9.67, 95% CI: 2.13–43.9, p < 0.001 and OR = 19.67, 95% CI: 2.53–102.9, p < 0.001, respectively). Number of patients with LQ of TNFα and IL4 gene’s CC/-CT-genotypes dominate over TT-genotype: 22.06%/26.47% versus 4.41% (χ² = 34.0, p < 0.001). The same trend found for IL1β. Lower IL1β production found in 35DelG genotype of CJB2 gene, compared to Non-Del-carriers by 30.35%; 63.16% versus 38.21% (χ² = 8.91, p = 0.003).

Discussion/Conclusion: Several polymorphisms of selected candidate genes are responsible for background conditions for IBD. IL4 gene’s C-allele (CC/-CT-) associate with lower TNFα; high or normal IL4, IL10, IL13 in 35DelG-genotype of CJB2 gene. IL4 hyperproduction in TT-genotype of IL4 gene form conditions for chronic inflammatory process. 35DelG mutation of GJB2 gene is characterized by increased production of TNFα, without significant growth of IL1β and hyperproduction of IL4, backed by activity of IL10, and IL13.
Efficacy of peroxisome proliferator-activated receptor gamma agonists for NAFLD/NASH is determined by genetic polymorphism of PPARγ gene

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Introduction: The initiating events in NAFLD/NASH relate to the development of obesity and insulin resistance. These promote hepatic free fatty acid flux which provides the appropriate entourage to develop NAFLD/NASH. Multiple studies showed that peroxisome proliferator-activated receptor gamma – NR1C3 (PPARγ) plays an important role in various biological processes including lipid and glucose metabolism. PPARγ has been implicated in the pathology of numerous diseases including obesity, diabetes, atherosclerosis, and cancer. PPARγ agonists have been used in treatment of different metabolic disorders and nonalcoholic steatohepatitis (NASH) normalizing glucose metabolism, decreasing steatosis, inflammation, and fibrosis. However, existing data is confusing, challenging efficacy of therapeutic use of PPARγ agonists.

Methods: The aim of the study was to clarify the perspectives for individualized therapy with thiazolidinediones depending on PPARγ Pro12Ala polymorphism. 249 patients with metabolic syndrome, hypertension, and dyslipidemia participated in the study. Among them 50 (20.08%) patients with NASH were selected to form study group. PPARγ agonist pioglitazone administered 30 mg daily during 50–51 weeks. Genetic polymorphism (Pro12, Pro12Ala, Ala12Ala) of PPARγ gene determined by PCR. Clinical examination and liver biopsies performed prior and after study.

Results: Genotypes distributions were as follows: Pro12 Pro (n = 32, 64.0%); Pro12Ala (n = 14, 28.0%); Ala12Ala (n = 4, 8.0%). Thiazolidinedione (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%) Ala12Ala 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 two subjects with Pro12Ala genotype, no other side effects were observed.

Discussion/Conclusion: We hypothesized that PPARγ agonists therapeutic efficacy is determined by respective genetic polymorphism of candidate gene. Administration of thiazolidinediones leads to metabolic and histologic improvement in most patients with NASH. However, as we found individual response may be affected by Pro12Ala polymorphism of PPARγ gene. This study shows that carriers of Ala genotype whilst comparatively rare among NASH patients are much less sensitive to PPARγ agonists' therapy. Our data partially explain the nature of failure for certain thiazolidinediones use and their risk of side effects (bladder cancer or hepatitis).
Targeting prostaglandins in cholangiocarcinoma: In vitro inhibition of cyclooxygenase-2 induces apoptosis and decreases proliferation of the human liver tumor cell

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Introduction: Recent studies showed that prostaglandin E₂ (PgE₂) is a potent activator of the Wnt signaling pathway implicated in regulation of developmental specification and regeneration. Wnt signaling is identified for its role in carcinogenesis and embryonic or/and stem cells development and differentiation. Following this idea, influencing arachidonic acid metabolism by means of cyclooxygenase-2 (COX-2) inhibitors may suppress growth of cancer cells and may have chemopreventive potential during cancerogenesis. However, it is still debatable whether COX-2 contributes to the malignant growth and whether inhibition of COX-2 modifies the malignant potential of liver tumors. The aim of the study was to clarify the pro-apoptotic and anti-proliferative effect of selective COX-2 inhibition.

Methods: Study performed experimentally on hepatocellular carcinoma cells lines HepG2/Hep3B, which were cultivated in modified media seeded onto well plates. Celecoxib 50 μmol/l added in study group cultures. Apoptosis related cytokines were analyzed by Western blotting. Apoptotic nuclei were visualized with the TUNEL-staining protocol and cells viewed with a fluorescence microscope (magn. x400). The number of apoptotic cells calculated in percentage of total nuclei.

Results: COX-2 inhibition related changes become evident in HepG2/Hep3B cell lines after 48 hours of treatment leading to a significant time-dependent reduction of cell numbers of up to 80% (p < 0.05). Cells became sparse, rounded, and detached from the dishes representing morphologic signs of apoptosis. This correlated with activation of caspase-9, caspase-3, and caspase-6 cytokines. However, exposure of cell cultures to 3 pg/ml PgE₂ eliminated the COX-2 inhibiting and pro-apoptotic effect on cells. This indicates that the antineoplastic properties of COX-2 inhibiting are dependent on reduces conversion of arachidonic acid to PgE₂ attributable to COX-2 inhibition.

Discussion/Conclusion: PgE₂ influences HCC cells, through canonical Wnt pathway that causes an accumulation of β-catenin in the cytoplasm and its eventual translocation into the nucleus to act as a transcriptional coactivator of transcription factors. Targeting metabolism of prostaglandins by selective inhibition of COX-2 causes marked growth inhibition of human liver tumor cells, based on the induction of apoptosis and inhibition of proliferation. The mechanism by which COX-2 inhibiting-related apoptosis is realized involves PgE₂ as found in this study but involvement of other factors into antiproliferative effect of COX-2 inhibitors remains unclear.
**IL10 polymorphism is associated with the immune response during CHB**

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**Introduction:** Interleukin 10 (IL10) is a pleiotropic cytokine produced by macrophages, T-helper 2 cells and B regulatory cells (CD5 subset, Breg) and can both stimulate and suppress the immune response. IL10 serum levels were found significantly elevated in chronic hepatitis B virus (CHB) patients. Recently it was suggested that the increased fraction of Breg cells might be the major source of elevated IL10 responsible for the suppression of HBV-specific cytotoxic T cell response and CHB pathogenesis. Here we analyzed the correlations between six SNPs in *IL10* gene and clinical parameters associated with CHB pathogenesis.

**Methods:** A cohort of 174 patients with CHB treated with interferon-α or nucleoside analogs was enrolled in the study. Six single nucleotide polymorphisms (SNPs) in *IL10* gene (rs18000871, rs1800896, rs1518110, rs1800872, rs1800893, rs3024490) were genotyped with MALDI-TOF mass spectrometry using Sequenom MassARRAY iPLEX platform and correlated with clinical parameters like: HBsAg presence, HBsAg loss, sustained virological response (SVR), liver fibrosis progression and liver inflammation grade.

**Results:** This study found that three SNPs in *IL10* gene (rs1800871, rs1800872, rs3024490) were associated with HBsAg seroclearance and liver inflammation grade in chronically infected patients. Minor alleles in IL10 rs1800871 (A vs. G), rs1800872 (T vs. G), rs3024490 (A vs. C) were associated with the increased HbsAg seroclearance. Minor alleles in rs1800871, rs1800872 and a major allele in rs3024490 were associated with an increased inflammation grade in the liver.

**Discussion/Conclusion:** Polymorphism in *IL10* gene might influence the immune reaction during the course of CHB by regulating CD8+ T cell response.
Deficiency of pH-sensing receptor TDAG8 ameliorates T-cell transfer colitis

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Introduction: The adaptive immune system plays a crucial role in the pathogenesis of inflammatory bowel diseases (IBD). Inflammation in IBD is typically associated with a decrease in local pH. The proton-sensing receptor T-cell death associated gene 8 (TDAG8), also known as G-protein-coupled receptor 65 (GPR65), has been identified as a risk gene for IBD in recent genome wide association studies. Therefore, we investigated the role of TDAG8 in T cell-mediated pathogenesis in intestinal inflammation using a murine adoptive transfer colitis model.

Methods: Naïve T-cells (CD4+CD62L+), from WT and TDAG8-/- donor mice, were injected into Rag-/- male mice. Injection of PBS was used in a control group. The results of colitis were evaluated by weight change, colonoscopy score, spleen weight, H&E staining, IHC and mRNA expression.

Results: Induction of colitis was observed after 3 weeks by weight loss, diarrhea and bloody stool. The WT group showed severe weight loss (p = 0.013), whereas the TDAG8-/- group displayed only a minor delay in weight gain. No significant differences were observed in colon length, spleen weight and colonoscopy score between PBS and the TDAG8-/- groups. H&E staining of distal and proximal parts of the colon showed severe infiltration and crypt damage in the WT group. The TDAG8-/- group displayed significantly less histopathological signs of colitis in comparison to PBS and WT groups. CD3+ and IL-17A immunoreactive cells were rarely detected in colonic tissue of TDAG8-/- in comparison to the WT group. Downregulation of mRNA expression of pro-inflammatory cytokines (IFNγ, TNF, IL-17A) was observed in the TDAG8-/- group in comparison with the WT group. No significant differences were observed in mRNA expression levels of Foxp3, RORg+ and IL-18.

Discussion/Conclusion: Our data demonstrate that TDAG8-deficiency in T-cells ameliorates the development of colitis suggesting an important physiological role of this pH receptor.
The health burden of primary biliary cholangitis in Switzerland – SwissPBC | SASL 36

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Introduction: Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease of unknown cause. Epidemiological data on PBC in Switzerland do not exist. The aim of our study is to assess the disease burden of PBC in Switzerland. This survey should be the basis for a prospective PBC registry in Switzerland.

Methods: This is a nationwide, cross-sectional, multicentre study involving also family doctors and gastroenterologists outside centres.

Results: About 500 patients can be recruited from the University Hospitals and hepatology centres. 43/295 gastroenterologists, 406/5004 general practitioners (GPs) answered the survey. 30 out of the 43 replying gastroenterologists have PBC patients, for a total number of 119 patients. 18 gastroenterologist are willing to participate, for a total number of 60 patients. 78 out of the 406 replying GPs have PBC patients, for a total number of 116 patients. 32 GPs are willing to participate, for a total number of 44 alive patients. About 50 PBC patients could be identified but are not available for the study because their physicians are not willing to participate. About 60 patients could be recruited from outside of centres.

Discussion/Conclusion: Patients recruitment will last until the end of June, data on the precise numbers of the recruited patients and analysis of the collected data will be presented.
Treatment of inflammation in excluded colonic departments

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Motivation: Chronic inflammation in the excluded departments of the colon and development of pathogenetically well-founded methods of preoperative preparation of patients for reconstructive-restorative operations are the topical issues of modern colorectal surgery.

Aim of the study: Optimization of the methods of preparation of excluded departments of the colon to reconstructive-restorative operations after subtotal colectomy (proximal or distal) for non-specific ulcerative colitis (UC).

Material and Methods: Whole 59 patients with UC undergoing surgery with disabling of distal colon from intestinal passage (2010–2015). From them 34 (57.6%) men and 25 (42.4%) women. Average age was 38.3 ± 10.2 (16–67) years. First group included 34 patients with moderately and significantly pronounced degree of colitis. Deadline for the shutdown of colon divisions amounted to 6–18 (9.9 ± 2.6) months, the length ranged 20–55 (29.5 ± 4.2) cm. Schema therapy was the introduction of a camomille decoction (t₀ ≤ 25 °C) twice a day. The second group included 25 patients with pronounced degree of colitis. The deadline for the shutdown of the colon divisions amounted to 12–18 (14.2 ± 3.5) months, the length ranged 22–70 (37.2 ± 7.2) cm. Additionally to first group, was included hydromassage with camomille decoction, endorectal injection of Lactulosae and introduction of Salofalk® suspension 4g/60ml at night. For solving of assigned tasks, was assured patients survey using clinical, laboratory and instrumental techniques as well as morphological biopsy from mucosal of disconnected divisions of the colon, bacteriological study of intestinal contents, determination of short-chain fatty acids fraction C2-C5-isomers in the mucosa of the large intestine divisions using the method of gas-liquid chromatographic analysis.

Conclusions:
1. Integrated approach in the treatment of colitis will include obligatory Salofalk® enemas and correction of intraluminal microflora (Lactulosae) for long time.
2. On the basis of the analysis of aggregate clinical, endoscopic and morphological changes in disconnected departments of colon, we recommend reconstructive-restorative operations at 6–12 months after stoma formation.
Dynamics of some immunological parameters during anti-TNF therapy of Crohn’s disease patients

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Introduction: Tumor necrosis factor (TNF) inhibitors are well-accepted treatment options for IBD, especially in case of steroid and classical immunosuppressive drug failure. However, few data are available for dynamics of fecal and serological biomarkers during anti-TNF therapy in Crohn’s disease (CD) patients. We aimed to follow up the variation of some immunological markers in order to evaluate the impact of anti-TNF therapy on them.

Methods: A total number of 57 CD patients at mean age 40 ± 15 (range 20–75 years) were monitored after initiation of anti-TNF treatment. Stool samples were tested for fecal calprotectin (FC) by quantitative automatic ELISA – Alegria and serum samples – for anti-neutrophil cytoplasmic antibodies (ANCA) by indirect immunofluorescence (IIF) and antibodies against Saccharomyces cerevisiae (ASCA IgA + IgG) by ELISA at the beginning and after 3–6 months follow-up on immunosuppressive therapy combined with anti-TNF agent.

Results: We observed that all of CD patients had significant decreases in levels of FC during anti-TNF therapy (from mean level of 963.97 mg/kg to mean level of 268.42 mg/kg; p = 0.043). Moreover, 75% of them have decreased levels of FC below the cut-off value (50 mg/kg). Positive for ASCA IgA/IgG were 17/24 tested patients but no differences were shown regarding application of anti-TNF therapy. However, the titers of pANCA had decreased in 2/5 patients and had not changed in 3/5 positive for pANCA patients after implementation of anti-TNF therapy.

Discussion/Conclusion: Initial and follow-up measurement of some immunological markers as FC, ANCA, ASCA, could be of beneficial for CD patients on anti-TNF therapy. However, a case-by-case joint decision taken with the clinical and histological improvement of patients should be considered.
The role of interleukin-24 in the pathomechanism of IBD-associated tissue remodeling

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Introduction: Intestinal fibrosis is a common and serious complication of IBD. Interleukin (IL)-24 is a member of IL-20 cytokine subfamily, involved in the regulation of inflammation, apoptosis or tissue remodeling in other organs. Increased mucosal level of IL-24 was described in the colon of patients with active IBD, however, its biological role is still poorly understood.

Methods: Effect of IL-24 on fibrosis-related gene expression and protein levels was determined in the colon of wild type and IL-24 receptor KO mice and also in human colonic fibroblast (CCD18-Co) and epithelial (HT-29) cells by real-time RT-PCR, western blot and flow cytometry, respectively.

Results: We found that IL-24 treatment altered the expression of fibrosis-related genes (COL1, COL3, FN1, MMP2, -9, TIMP1, -2), increased the level of pro-fibrotic factors (TGFβ, PDGF-B) in the colonic mucosa of mice and in human colonic epithelial and fibroblast cells. Lack of IL-24 in KO mice with dextran sulfate sodium-induced colitis resulted in decreased expression of pro-fibrotic factors.

Discussion/Conclusion: IL-24 may promote tissue remodeling shifted toward an excessive deposition of extracellular matrix components directly by acting on fibroblasts and indirectly via induction of pro-fibrotic factors of epithelial cells. Our data suggest that inhibition of IL-24 may have a significant anti-fibrotic effect.

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The effects of UDCA in the treatment of NASH

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Introduction: Non-alcoholic steatohepatitis (NASH) is a condition that occurs during the progression of non-alcoholic fatty liver disease and if untreated can lead to liver cirrhosis. NASH has become one of the most common liver-related health problems. Effective therapy for NASH is still lacking. Ursodeoxycholic acid (UDCA) has been reported to be of benefit based in several randomized clinical trials.

Methods: In this study, we investigated the efficacy of UDCA in the treatment of NASH. A total of 34 patients with liver biopsy-proven NASH were treated with 15 ± 2 mg/kg/daily dose. Male and female patients 20 to 70 years of age with NASH were included. Clinical symptoms and biochemical parameters were controlled every 3 months and liver biopsy was performed after minimum 24 months of the therapy.

Results: UDCA improved clinical symptoms in 31 out of 34 patients and biochemical markers of hepatocellular damage (GGTP, AST, ALT, alkaline phosphatase, and serum bilirubin level) in 27 out of 34 patients. The beneficial effect of UDCA on the liver histology was assessed in 19 out of 34 patients after minimum period of 24 months of therapy. Improvement was found only in 10 out of 34 patients.

Discussion/Conclusion: The data from this study suggest that UDCA therapy is effective, safe and well tolerated in the treatment of patients with NASH. UDCA was associated with an improvement in serum liver biochemistries and some of histological features.
Evaluation of fibrosis and inflammation parameters of the liver in patients with diagnosed cystic fibrosis – Preliminary study

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Introduction: Liver lesions in the course of cystic fibrosis are a group of complex interactions of the processes of fibrosis, inflammation, re-modelling, apoptosis and cholestasis. Despite the fact that they affect only 5–20% of patients with diagnosed cystic fibrosis, they increase the mortality rate, shorten the survival rate and worsen the quality of life.

The aim of the study was to evaluate selected parameters of the liver fibrosis and inflammation in patients with diagnosed cystic fibrosis.

Patients and Methods: 43 patients were evaluated (24 girls and 19 boys), aged from 13 months to 17 years (mean age 6 years) with diagnosed cystic fibrosis. Activity of alanine and aspartate aminotransferases, alkaline phosphatase, γ-glutamyltranspeptidase, concentration of albumin, bilirubin, α-macroglobulin, A1 apolipoprotein and haptoglobin in the blood were evaluated. Index Fibrotest and Actitest were calculated on the basis of these parameters.

Results: Increased activity of ALAT was observed in 6/43 patients (13.9%) and GTP in 6/43 (13.9%) children too. Elevated concentration of α2-macroglobulin was until in 25/43 children (58.1%), its correlated with abnormal result of Fibrotest Index (F1-F2) in 5 patients. All children with abnormal Fibrotest Index had increased concentration of α2-macroglobulin in the blood. Increased concentration of A1 apolipoprotein in the blood was found in 8/43 children, this parameters correlated with abnormal results of Fibrotest and Actitest Index only in 2 patients. Increased concentration of haptoglobin in the blood was observed only in 9/43 children, results didn’t correlate with abnormal results of Fibrotest and Actitest Index. Ultrasonography examinations of the liver and bile ducts were normal in 4/5 patients with abnormal result of Fibrotest Index.

Conclusion: Determination of Fibrotest and Actitest Index can be helpful in detection of early changes in the liver in patients with diagnosed cystic fibrosis.
Potential non-invasive biomarkers of liver fibrosis in chronic hepatitis B infection

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Introduction: Chronic liver disease progresses through different pathological stages that vary from mild hepatic inflammation without fibrosis to advanced hepatic fibrosis and cirrhosis. Hepatitis B virus (HBV) infection is the leading cause of liver cirrhosis, with about 20–30% of chronically infected adults developing cirrhosis and/or hepatocellular carcinoma. A liver biopsy has been considered as the gold standard for assessing liver histology. However, increasing awareness of its several drawbacks has questioned its accuracy and value in clinical practice. Therefore, the aim of this study was to find new noninvasive markers for assessing risk of liver fibrosis in HBV-infected patients that could be used in clinical practice.

Methods: The study group consisted of 174 HBV-infected patients. We have chosen 14 single nucleotide polymorphisms (SNPs) in 3 genes involved in HBV life cycle in hepatocytes: rs7154439, rs4646287, rs2296651 in solute carrier family 10 member 1 (NTCP/SLC10A1), rs553717, rs2352028 in glypican 5 (GPC5) and rs1129644, rs11559067, 3087943, rs707887, rs1047782, rs2294689, rs17249952, rs17249973, rs3212230 in tyrosyl-DNA phosphodiesterase 2 (TDP2). All SNPs were genotyped by MALDI-TOF mass spectrometry (MS).

Results: No association was found between SNPs in NTCP gene and the liver fibrosis progression. The liver fibrosis stage was more severe in patients who had major alleles in TDP2 (rs1129644). On the other hand, the major alleles in GPC5 (rs553717, rs2352028) were a good prognostic factor, and were more frequently found in patients with mild score of fibrosis or no fibrosis.

Discussion/Conclusion: This the first study that indicates the association between TDP2 and GPC5 polymorphisms and liver fibrosis progression. However, further validation studies including a broader group of patients are needed to confirm our findings.
The results of combined treatment of Helicobacter pylori associated stomach MALT lymphoma

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The purpose was to study of effective variants of combined treatment for MALT-lymphoma of the stomach (MALTS).

Materials: We analyzed the results of treatment 75 patients with MALTS. Men was – 26 (35.3%), women – 47 (64.7%). According to Lugano classification (1993), 1st stage was in 49 (65.3%) patients, IIE – in 10(13.3%), II1 – in 11(14.6%) and II2 – 5 (6.6%). In 63 (84.0%) during the examination revealed the presence of infection with Helicobacter pylori (Hp) different degrees of contamination. However, from them in 13 (37.1%) patients due to the presence of functional gastric complications (bleeding and stenosis) being performed gastrectomy with lymph node dissection to D2. Postoperatively, these patients underwent adjuvant chemotherapy (ChT). In 6 (17.1%) (Hp-negative) patients were only ChT, the remaining 16 (45.8%) patients (Hp-positive) was performed ChT with anti-Hp therapy (triple-therapy).

Results: In the early postoperative period in 2 (10.5%) (p > 0.05) patients had complications: 1 (5.2%) – postoperative pancreatitis and in 1 (5.2%) – wound abscess. After chemotherapy in 9 (31.0%) patients observed side effects of chemotherapy I- and II-degree of toxicity that stopped inclusion in the arsenal of treatment of symptomatic therapy. After chemotherapy with anti-Hp therapy in 2 (13.3%) patients observed side effects of chemotherapy I-toxicity. Indicators of a one-year survival rate in the groups were almost identical: 96.5% – after the surgery + chemotherapy, 93.1% – after ChT and 100% – after chemotherapy + anti-Hp therapy (p > 0.05). However, the 3-year indices were slightly different, representing 86.2%, 79.3% and 86.6%, correspondingly (p > 0.05). Patients after surgery + ChT and ChT + anti-Hp therapy during the 40-month observation of relapse is not established. After chemotherapy from 29 in 5 (17.2%) had recurrent disease in the period from 13–28 months that required repeated courses of chemotherapy with the inclusion of anti-Hp therapy.

Conclusion: Our modest analysis shows that the appropriateness of a combined approach in the treatment of MALTS. Thus, performance of surgical component, followed by using of adjuvant chemotherapy does not degrade performance of remote results. We consider it necessary to further explore the possibility of anti-Hp therapy in these patients, because of its use in combination with chemotherapy gives promising results in the treatment of MALTS.
The assessment by USG Doppler study results of treatment in 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. Numerous Doppler and USG symptoms (hepatomegaly, veins dilatation, decrease of the respiratory movements of the vena cava inferior (IVC), liquid inside visceral cavities, pathological vessels spectra, and others) have clinical significance for grade hepatic hyperemia. To observe and assess results after clinical treatment may have prognostic significance.

Patients and Methods: 35 patients suffering from cardiac failure (III–IV NYHA classification) with chronic insufficiency of tricuspid valve were observed clinically. All patients were examined by USG Doppler method before and after clinical treatment. Results of examination were compared to clinical observation – physical examinations, period of disease, laboratory tests, cardiac sonography, X-ray examination. Others liver diseases were excluded.

Results: Pathological USG results typical for liver hyperemia were observed in 30 patients. After treatment the reduction or elimination symptoms important for clinical prognostic grade were observed in 12 patients: IVC and/or hepatic veins diameter reduction, respiratory IVC movement increase, decreased or elimination liquids from body cavities, different positive changes of spectral flow portal and hepatic veins, others.

Comments: The hepatomegaly, veins dilatation, decrease of the respiratory movements of the IVC, gall bladder wall thickness, liquid inside visceral cavities are typical USG symptoms for liver congestion. The presence of the hepatic veins flow abnormality, reflexes abnormal liver – heart relations come across in advanced right 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. The liver reaction after diuretic therapy may be used as prognostic factor in clinical observation.
2. Some symptoms of advanced hyperemic liver (thick gall bladder wall, biphasic hepatic and/or portal vein spectrum) are changeless after clinical treatment.
3. The relationship between clinical and USG Doppler reaction after the treatment not always are equal.
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