Gut-Liver Interactions: From IBD to NASH

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GUT-LIVER INTERACTIONS:
FROM IBD TO NASH

Innsbruck, Austria
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Scientific Organization:
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M.P. Manns, Hannover (Germany)
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Session I

NAFLD
Pathophysiology of NAFLD

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Unhealthy lifestyles and genetic factors synergistically contribute to NAFLD. A high-calorie diet, leading to weight gain, obesity and eventually type 2 diabetes is probably the main driver for hepatic fat accumulation, via insulin resistance. The role of individual nutrients is less defined; excess intake of fats (mainly saturated fats), refined carbohydrates, sugar-sweetened beverages, and, in general, the Western diet have all been associated with obesity and NAFLD. Liver fat accumulation is largely dependent from fat stores; the majority of hepatic triglycerides come from recirculation of fatty acids from visceral adipose tissues, driven by insulin resistance, or from de novo lipogenesis. Liver fat accumulation becomes thus part of a generalised lipotoxic disease of non-adipose tissues, also accounting for fat accumulation in the heart, islet cells and muscles, dictating disease progression and patients’ outcomes. The disease is mediated by a variety of counterbalancing adipokines, namely leptin and adiponectin, and by several cytokines contributing to disease progression. The role of diet and behavior is also supported by studies showing that any amount of weight loss reduces liver fat, improves hepatic and peripheral insulin resistance and may lead to NASH resolution, as also reported in intervention series of bariatric surgery. Finally, the possibility of a gut-liver interaction has been postulated, again mediated by obesity-associated factors.

Several genetic modifiers of NAFLD are also present and mediate disease development and progression, but a minority have been robustly validated. The best-characterised genetic association is with PNPLA3, initially identified from genome wide association studies and confirmed in multiple cohorts and ethnicities across the entire histological spectrum of NAFLD. The gene variant is responsible for a loss of function that impairs triglyceride hydrolysis and also stimulates de novo lipogenesis. As such, it also increases the risk of cardiovascular morbidity. Another gene, the TM6SF2 has been recently reported as disease modifier, interfering with lipoprotein secretion and assisting in risk stratification for liver-related morbidity.
Extrahepatic diseases and NAFLD: The triangular relationship between NAFLD, type 2-diabetes and dysbiosis

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Key words: non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2DM), dysbiosis, obesity, insulin resistance

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Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases from simple steatosis with hepatic lipid accumulation to end stage liver disease with decompensated cirrhosis, liver failure and hepatocellular carcinoma. Recent data from the USA showed that in 2013, NAFLD was the second most frequent indication for liver transplantation behind Hepatitis C. Since there are now effective treatments for Hepatitis C and there is currently no licensed treatment for NAFLD, it has been predicted that over the next 10–15 years, NAFLD will replace Hepatitis C as the most frequent indication for liver transplantation. Besides, increasing the risk of hepatocellular carcinoma and end stage liver disease, recently it has become clear that NAFLD also increases risk of extrahepatic diseases such as type 2 diabetes (T2DM), cardiovascular (CVD), cardiac diseases and chronic kidney disease, to name but a few. Of each of these extrahepatic diseases, the evidence to date suggests that NAFLD is a strong risk factor for T2DM. When NAFLD occurs in combination with obesity and insulin resistance (as it frequently does), there is a marked increase in risk of incident T2DM with possible synergism occurring between liver fat accumulation, insulin resistance and obesity, to further increase risk of development of T2DM. When T2DM develops, there is a further increase in risk of progression of liver disease to liver fibrosis. Thus, there is a reciprocal relationship between NAFLD as a risk factor for T2DM, and T2DM as a risk factor for liver disease progression in NAFLD. Moreover, recent evidence now points to the importance of perturbation of the intestinal microbiota (dysbiosis) in both T2DM and NAFLD. Consequently, there is a triangular relationship between dysbiosis-T2DM-NAFLD. This presentation/review with focus on T2DM as a key extrahepatic complication of NAFLD. The presentation/review will describe and discuss the triangular relationship between dysbiosis-T2DM-NAFLD and the factors and potential mechanisms underpinning this relationship.
**How to diagnose NAFLD**

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Most patients with Non Alcoholic Fatty Liver Disease (NAFLD) are asymptomatic and present with either unexplained abnormal liver blood tests or a bright liver on ultrasonography. Most patients will have normal liver blood tests raising the issue of whether patients with risk factors for NAFLD (diabetes and/or metabolic syndrome) should be screened for its presence with biomarkers, such as the Fatty Liver Index (FLI). The diagnosis of NAFLD requires the exclusion of all other causes of chronic liver disease and other causes of steatosis, in particular heavy alcohol consumption and viral hepatitis particularly HCV genotype 3. Diagnostic work-up should include evaluation of family and personal history of components of the metabolic syndrome and assessment of liver tests, fasting blood glucose, triglycerides and HDL levels. A drug history is important due to a number of drugs being associated with steatosis. To confirm the diagnosis of NAFLD and quantify the amount of steatosis ultrasound and MRI based techniques are available, but none are in routine use outside clinical trials and standard ultrasound is no more accurate than biomarkers such as FLI. The accurate staging of NAFLD requires liver biopsy, however, this is clearly impractical for such a prevalent disease. Accordingly a number of imaging and blood based biomarker tests have been evaluated. While none have proved reliable for the diagnosis of Non-alcoholic steatohepatitis (NASH), several have proved accurate in diagnosing the presence of stage 3 or 4 fibrosis, including the NAFLD fibrosis score (NFS) fibrosis-4 (FIB-4) and the enhanced liver fibrosis (ELF) test. Of the imaging techniques elastography has received the most attention and is being used in routine clinical practice. Ultrasound (ARFI) and MR-based elastography (MRE) has recently been described but, as yet, none are sufficiently accurate to replace liver biopsy for clinical trials or cost-effective for use in routine clinical settings.

**Reference:**

Treatment of NAFLD

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Non-alcoholic fatty liver disease represents on an evolution scale a new disease. It is driven by a gap between our physiology and our lifestyles. For millions of years life meant moving to find scarce food. Now, we do not have time for physical activity and we are constantly exposed to high-caloric nutrients. It follows that changing lifestyles should be the first measure discussed with patients suffering from NAFLD. This is not only the most physiological treatment but also a therapy with high benefits for low costs. This approach should address the lack of physical activity, the overweight, the diet, not to mention the drinking, smoking and sleeping habits. Few patients succeed; it is hard to change lifestyles. In reality, it is easier to take a medication. Ursodeoxycholic acid has been tested in randomized control trials and the results are negative. Agonists of the peroxisome proliferator-activated receptor (PPAR) gamma have demonstrated beneficial hepatic effects in randomized controlled trials, but these drugs have side effects limiting their force of attraction. Vitamin E, which has antioxidant properties improved non-alcoholic steatohepatitis in non-diabetic patients. This drug is cheap, but it has also been suggested to be associated with side effects. New treatments are on the horizon with recent randomized controlled trials showing interesting effects with obeticholic acid, an FXR agonist, and elafibranor, a dual PPAR alpha-delta agonist. Other drugs aiming at apoptosis and fibrosis are also considered in this indication. The definition of the endpoints for phase 3 clinical trials is one of the most important challenges the field is currently facing.
Session II

Alcoholic liver disease
Acute alcoholic steatohepatitis (ASH) is a heterogenous condition that is clinically and pathophysiologically characterized by severe hepatic inflammation and associated with high mortality rates. In the western world, the condition occurs in the majority on the background of established cirrhosis. Histopathologically, the condition is characterized by severe steatosis with superimposed neutrophilic infiltration, hepatocyte balloon degeneration, deposition of Mallory’s hyaline and varying degrees of cholestasis. Diagnosis of the condition is made in the context of patients with either known or undiagnosed cirrhosis presenting within weeks of an alcohol binge with jaundice and evidence of systemic inflammatory response. Histology is required for diagnosis as clinically it is not possible to diagnose ASH from other causes of acute deterioration such as infection. Huge controversy exists in factors defining prognosis of patients and various scoring systems have been defined, all of which have severe constraints. In general, the severity of individual organ dysfunction is associated with prognosis. Animal models are not representative of the clinical syndrome and extrapolation of data from animal models to therapeutic intervention is not appropriate. Steroids, or anti-inflammatory agents targeting inflammation have not been shown to be universally effective and cannot be recommended for routine use arguing also against hepatic inflammation being the primary cause of the syndrome. Immune failure and infection are common in ASH and a common cause of progression to acute on chronic liver failure and, high mortality rates. In order to find new therapeutic targets for therapy, a new look at systems biology approaches to consider genetic predisposition, bacterial translocation, the microbiome, nutrition and immune responses are necessary to start to unravel the pathophysiological mechanisms involved. Because of the lack of suitable animals models means that the studies will have to be performed in patients making the task more difficult.
Co-morbidities in ASH

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Alcohol use disorder is a main cause of preventable morbidity and mortality worldwide. There is a clear link between alcohol use and neuropsychiatric disorders (e.g., depression, post-traumatic stress disorder, etc), as well as social isolation. Alcohol is highly diffusible through cell membranes and is metabolized by most tissues. Thus, its toxicity affects most organs. Because the liver is the main site of alcohol metabolism, it is the most frequently affected organ among adults with prolonged ethanol intake. In fact, advanced alcoholic liver disease (ALD) is the main cause of liver-related mortality. In clinical practice, many patients with presumed ALD have other etiological agents that can act synergistically with alcohol to cause liver injury and fibrosis, favoring the development of cirrhosis and HCC. These causes include hepatitis B and C, metabolic syndrome and hemochromatosis. For example, patients with high-risk alcohol consumption and obesity have almost two-fold risk to develop cirrhosis and increased risk for HCC.

In patients with ALD, co-morbidities associated to permanent alcohol abuse are frequently seen. First, patients often have signs of central and peripheral neuropathy and in some cases Wernicke-Korsakoff syndrome is seen. In the pancreas, toxic metabolites of alcohol cause acinar cell injury leading to pancreatitis and subsequent fibrosis, yet severe pancreatitis typically does not associated with liver disease. Dilated cardiomyopathy and various arrhythmias are also associated with alcohol abuse. In the kidney, alcohol abuse is associated with glomerulonephritis, acute nephropathy and kidney graft failure. Other comorbidities include malnutrition, vitamin deficiencies, non-immune hemolytic anemia and muscle wasting due to alcoholic myopathy. Therefore, the integral care of the patient with ALD ideally requires a multidisciplinary approach. Finally, the cause of death after transplantation for ALD differs compared to non-ALD recipients. In particular, cardiovascular causes and de novo malignancies in the aero-digestive tract are significantly over-represented in the patients transplanted for ALD. There is not a clear association between new-onset cancers and alcohol relapse, suggesting that other environmental factors such as cigarette smoking and obesity certainly play a role.

In conclusion, patients with ALD often have co-morbidities due to prolonged alcohol misuse. A careful evaluation of psychosocial problems, the nutritional status as well as the potential damage of other organs should be performed as part on the integral care of these patients.
Treatnent of alcoholic hepatitis

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Several investigators have given priority to treatment of severe alcoholic hepatitis (Maddrey score $[DF] \geq 32$), as this entity is associated with significant early mortality. American and European guidelines for alcoholic liver disease recommend the use of prednisolone or pentoxifylline in patients with severe alcoholic hepatitis. A multicentre randomized double-blind trial of 1103 patients conducted in the UK with 2-by-2 factorial design revealed a reduction in mortality at 28 days in patients treated with prednisolone compared to controls whereas Pentoxifylline did not improve 28-day-survival. However, survival benefit in prednisolone treated patients was not sustained at 90 days. Data from this trial and previous studies has been incorporated into a network meta-analysis which observe that there is a short term benefit from corticosteroid treatment. Corticosteroid treated patients had an early and greater improvement of liver function and a better response to the assigned therapy assessed by the Lille model. Early identification of responders with a substantial improvement in hepatic function an advance in the management of severe AH. After 7 days of treatment, physicians may identify responders to medical therapy using a model, referred to as the Lille model. The approach using the Lille model highlights the benefits obtained from strategy integrating the impact of treatment upon the evaluated endpoint. The probability of acquiring infection after corticosteroids had been started was drastically lower in responders (Lille model < 0.45) compared with non-responders. At first glance, infection might be considered a major factor contributing to death. However, it is not an independent prognostic factor, and early response to therapy seems to be more important for predicting both survival and the clinical significance of infection. The most likely hypothesis is that early improvement in liver function is the most important factor contributing to decreased risk of infection, and to patient survival. A recent study observed that combinative therapy with pentoxifylline and prednisolone was not superior to prednisolone alone although incidence of hepatorenal syndrome was less frequent in patients treated with combination therapy. Recent study suggested that early liver transplantation may be an appropriate rescue option for rare patients with a first episode of severe alcoholic hepatitis not responding to medical therapy. However, early liver transplantation is relevant only for a minority of patients whereas new therapeutic strategy are urgently need for the majority of non-responders in order to improve the outcome of patients with this life-threatening disease.
ASH and NASH: A relevant association

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Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are the most frequent chronic liver disease, and their advanced forms alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH) are the most frequent conditions leading to elevated liver enzymes and liver cirrhosis, respectively, in the Western world. Both ALD and NAFLD cause hepatic steatosis, which can be considered as the first pathological step in the disease cascades. Still, only a fraction of patients further develop significant hepatic inflammation (ASH or NASH), and even less progress to significant hepatic fibrosis and cirrhosis.

Although the cause of the development of fatty liver in ALD and NAFLD is different, there is increasing evidence that ALD and NAFLD share at least some pathophysiological mechanisms in their development and progression. Alcohol as well as dietary lipids are predominantly metabolized in hepatocytes, rendering interactions between alcohol- and lipid-metabolism very likely. Truly, clinical studies propose a causative link between the consumption of alcohol and progressive liver disease in obese individuals. However, it is incompletely understood how alcohol and obesity and other components of the metabolic syndrome interact and whether the combined pathological effects are additive or synergistic. We have developed in vitro and in vivo models to study isolated as well as combined effects of alcohol and steatosis in primary human hepatocytes and rodents. Here, we observed synergistic pathological effects of alcohol and steatosis on hepatocellular injury as well as inflammation and fibrosis, respectively. However, we also observed that the alcohol-steatosis connection triggers hepatoprotective mechanisms such as autophagy. One may speculate whether individual factors tipping the balance on the one or the other side of detrimental or beneficial joint effects of alcohol and (non-alcoholic) steatosis account at least in part for the high variation in the clinical course of alcoholic liver disease. In addition to direct effects on the liver, the view has to be expanded to other organs affected by chronic alcohol consumption or the metabolic syndrome, to understand also extrahepatic interactions such as on the intestinal barrier, which may indirectly affect hepatic injury. Undoubtedly, alcohol and the metabolic syndrome appear as a dangerous mix, and there are important interactive effects of either condition with regard to crucial triggers of liver injury.
Session III

PBC/PSC
The etiology of primary sclerosing cholangitis (PSC) involves heritable factors. Over the last 5–10 years, the application of unbiased genome-wide association studies in large collections of unrelated cases and healthy controls have revealed an overall picture of the susceptibility architecture of complex liver diseases including PSC. The main observation is that of intertwined roles for genetic and environmental risk factors, perhaps with the environmental factors representing the dominating drivers of disease. However, elucidation of genetic risk may guide the identification of critical environmental co-variables. In addition, there is clear evidence for shared pathophysiological pathways not only representing a basis for the co-occurrence of PSC with other typical autoimmune diseases, but also supporting the classification of PSC as an autoimmune disease. Hopefully, overlapping genetic risk factors may allow re-purposing of drugs in similar diseases and provide new treatment options in a rare disease like PSC. The strong clinical relationship between PSC and inflammatory bowel disease (IBD) is also in part explained by overlapping genetic architectures. However, the observed genetic differences between PSC and IBD highlight that PSC is a disease condition distinct from and not merely a complication to IBD. Finally, recent genetic studies show that the well-known clinical heterogeneity in PSC is reflected in the genetic profile of the patients, suggesting that the most influential disease mechanisms may vary between individuals. This is important to take into consideration in future strategies of personalized medicine.
The mucosal immunity of PBC and PSC

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Overt hepatobiliary injury in the context of dysregulated mucosal immunity is perhaps best highlighted clinically in primary sclerosing cholangitis (PSC), wherein the vast majority of patients develop concomitant inflammatory bowel disease (IBD). This clinical observation has stimulated several intriguing pathogenic concepts, in which a divergent enteric microbiome, defective mucosal immune tolerance, and disrupted epithelial barrier functions are all implicated in liver injury. That particular gene-polymorphisms confer combined susceptibility to intestinal inflammation and biliary epithelial injury underscores the fundamental role of mucosal immunogenicity in combined disease pathogenesis. Moreover, immunopathogenic IL-17 responses, which are implicated in the pathogenesis of almost all human autoimmune diseases including PSC and primary biliary cirrhosis (PBC), can be redirected from the periphery to the small intestine via recruitment pathways that are also common to inflamed biliary epithelium. Additionally, the discovery of long-lived mucosal memory T-cells being recruited to the liver in response to aberrantly expressed endothelial adhesion molecules and chemokines, which are normally 'gut-restricted,' affords a further plausible explanation as to why immune-mediated biliary injury is commonly associated with intestinal inflammation.
Cancer risk and PSC

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Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease mainly affecting young male patients. PSC is characterized by a chronic inflammation and fibrotic strictures of the intra- and extrahepatic biliary system, which eventually lead to cholestasis and biliary cirrhosis. However, the clinical course remains highly variable. As the etiology remains unknown, the development of a causative treatment is challenging and today no specific medical therapy is available. Ursodeoxycholic acid has been widely used for the treatment of PSC, but improved only biochemistry and/or symptoms in low- or medium dosages and is probably harmful in higher dosages. The endoscopic therapy encompasses balloon-dilatation and/or stenting of strictures, relieves clinical symptoms and improves a cholestatic enzyme profile. However, endoscopic therapy is limited to patients in advanced stages of PSC with biliary obstruction.

PSC is associated with a >160-fold increased risk to develop hepatobiliary malignancies. Therefore, PSC is the most common predisposing condition for cholangiocarcinoma (CC) in Western countries. The chronic inflammatory process contributes to the pathogenesis of CC in PSC. In patients with PSC, the differentiation between benign and malignant strictures is particularly difficult because CC as well as chronic or acute inflammation may result in similar cholangiographic findings. The prognosis of CC remains poor as curative treatment options such as surgery or orthotopic liver transplantation can only be performed at an early stage of CC. Unfortunately, CC is often detected in an unresectable stage as specific tumor markers or other reliable diagnostic methods are still lacking. In clinical practice, the diagnosis of CC is based on a combination of imaging techniques and tissue sampling. Tumor markers, like serum carbohydrate antigen 19-9 (CA 19-9), have a low specificity and sensitivity as CA 19-9 is also elevated in patients with benign cholangitis. Therefore, new strategies for surveillance and detection of CC of patients with PSC are needed.
Therapy of PBC and PSC

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Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) represent the two major chronic cholestatic liver diseases. Their pathogenesis differs, but their clinical course, major symptoms and long-term prognosis without therapeutic interventions show striking similarities. Here, we summarize the actual guideline-recommended treatment of PBC and PSC as well as future therapeutic options. Immunosuppressive/immunomodulating interventions aiming to minimize immune-mediated damage in PBC and PSC have disappointed in the past. New approaches are beyond the scope of this short overview.

PBC
Today, ursodeoxycholic acid (UDCA, 13–15 mg/kg/d) is recommended for treatment of all patients with PBC provided that they show abnormal serum liver tests. UDCA is a mainly postranscriptionally acting secretagogue in hepatocytes and cholangiocytes. UDCA improves serum liver tests, halts fibrosis and delays development of complications of cirrhosis. Overall life expectancy has become normal in two of three PBC patients treated with UDCA. Still, one in three patients will need additional therapeutical interventions in order to reach normal life expectancy at an acceptable level of quality of life.

A number of nuclear receptor agonists are tested in combination with UDCA in phase 3 studies, and the study results will be published in the near future. Farnesoid X receptor (FXR) agonists such as the bile acid (BA) derivative obeticholic acid (OCA, 6-ethyl-chenodeoxycholic acid; 5–10 mg/d) and the non-BA PX-102 are tested in phase 2 and phase 3 trials and showed promising results in first analyses. Final publication of the first multicentre phase 3 study with OCA is awaited. The major side effect of OCA, pruritus, seems to be manageable at low starting doses of 5 mg/d. The corticosteroid budesonide has also been studied in combination with UDCA in a phase 3 trial in PBC patients not adequately responding to UDCA, the results of this trial are expected shortly.

The peroxisome proliferator-activated receptor (PPAR) agonists bezafibrate and fenofibrate in combination with UDCA have been shown to consistently improve serum markers of cholestasis in PBC patients not adequately responding to UDCA alone, but their long-term effects on prognosis remain unclear. Results of a phase 3 trial are awaited.

Study results of the potential beneficial effects of inhibitors of the ileal apical sodium-dependent bile salt transporter (ASBT) remain to be awaited.

Liver transplantation in end-stage disease remains the only potentially curative treatment in PBC.

PSC
UDCA has been shown to improve serum liver tests including surrogate markers of prognosis such as serum alkaline phosphatase and bilirubin at moderate doses of 13–20 mg/kg/d and may lower disease progression, but long-term efficacy still remains
uncertain\textsuperscript{2,5}. At very high doses, UDCA (28–30 mg/kg/d for 5 years) was harmful in that more patients developed varices or were listed for liver transplantation than placebo-treated patients, although serum liver tests improved\textsuperscript{6}. 

24-norursodeoxycholic acid (norUDCA) is a side-chain shortened UDCA derivate which lacks a methylene group resulting in a relative resistance to amidation with taurine or glycine compared with UDCA. norUDCA is a potent bicarbonate secretagogue in humans. A large phase 2 trial is just terminated, the results are awaited. Other therapeutic possibilities are limited for PSC. FXR agonists such as obeticholic acid (OCA) can be considered but FGF19 induction by these agonists may be a caveat. FGF19 has proliferative properties; thus, effects on cholangiocarcinogenesis in PSC have to be carefully considered during long-term administration. For the FGF19 derivative NGM282, which has a 95% homology with FGF19, the lack of a proliferative effect when compared to FGF19 may provide an advantage; NGM282 administered subcutaneously is tested in a phase 2 study in PSC. The PPAR agonists bezafibrate and fenofibrate improved serum markers of cholestasis not only in PBC, but also in PSC; still, their long-term effects remain unclear. Endoscopic treatment of dominant bile duct strictures of the large bile ducts by balloon dilatation/short-term stenting in advanced PSC is regarded as standard of care\textsuperscript{2,5}. Liver transplantation remains the only potentially curative treatment in PSC\textsuperscript{2,5}.

References:
Session IV

Gut-liver interactions: From microbiota to immunity
State-of-the-Art

Gut microbiome analyses for diagnosis and targeted treatment

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The importance of the gut microbiota for regulation of metabolism and immune functions is well established, and evidence has been presented that the gut microbiota may also affect behavior. However, the exact molecular mechanisms by which bacteria in the gut exert their actions still remain elusive. Our laboratory is involved in large-scale metagenomics projects in collaboration with BGI-Shenzhen using high throughput Illumina-based sequencing of total fecal DNA. The projects are in particular focused on characterizing changes the gut microbiota associated with metabolic disorders, cancers and autoimmune diseases. In this lecture I will summarize our recent results demonstrating how metagenomics analyses can be used for early non-invasive diagnosis of colorectal cancer, describe examples of how such analyses can be used to predict efficacy of treatment in relation to rheumatoid arthritis, and even stratify type 2 diabetic patients prior to start of treatments. I will conclude the lecture by discussing the perspectives of these findings.
Iron and innate immunity

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The transition metal iron plays a pivotal role in host-pathogen interaction because mammalian cells and microbes have an essential demand for the metal, which is required for many metabolic processes and for microbial pathogenicity. In addition, cross-regulatory interactions between iron homeostasis and immune function are evident. Cytokines and the acute phase protein hepcidin affect iron homeostasis leading to the retention of the metal within macrophages. This is considered to result from a defense mechanism of the body to limit the availability of iron for extracellular pathogens while on the other hand the reduction of circulating iron results in the development of anemia of inflammation. Opposite, iron as well as the anemia inducible hormone erythropoietin affect innate immune responses by influencing IFN-γ mediated (iron) or NF-κB inducible (erythropoietin) immune effector pathways in macrophages. Thus, macrophages loaded with iron lose their ability to kill intracellular pathogens via IFN-γ mediated effector pathways such as nitric oxide (NO) formation. The interaction between the NO pathway and iron homeostasis became even more evident by the observation that cytokine inducible formation of NO increases the expression of the cellular iron exporter ferroportin thereby reducing the availability of iron and thus the proliferation of intramacrophage bacteria, a strategy for which the name nutritional immunity was coined. Of note, the reduction of intracellular iron availability strengthens macrophage effector pathways such as the formation of NO, TNF-α or IL-12 while IL-10 expression, an anti-inflammatory cytokine regulated by iron availability, is impaired. Of note, iron mediated control of innate immune function and T-helper cell differentiation can also affect disease activity in auto-immune disorders such as rheumatoid arthritis or IBD.

Finally, certain innate resistance genes such as natural resistance associated macrophage protein (Nramp1), lipocalin-2 or calprotectin exert part of their antimicrobial activity by controlling host and/or microbial iron homeostasis. Nramp1 pumps iron out of the microbial containing phagolysosome and in doing so it increases anti-microbial immune effector function of macrophages directed against intracellular microbes. The neutrophil derived protein calprotectin sequesters iron in the extracellular environment whereas lipocalin-2 scavenges iron loaded siderophores originating from certain Gram-negative bacteria, but lipocalin-2 is also able to shuttle iron across cell membranes making use of a mammalian siderophore. However, the latter process may differently affect the outcome of infection depending on the primary localization of a microbial pathogen (intracellular and extracellular) and thus different immune mediated strategies to control iron access for microbes have evolved during evolution.

In summary, several cross-regulatory interactions between iron homeostasis and immune function exists which mainly arise from the essential role of iron in host-pathogen interaction. However, a deeper insight into these processes is of pivotal importance in the management of subjects with IBD specifically when evaluation the potential risks and benefits of iron supplementation strategies.
Selected references:


Session V

Evolving IBD pathogenesis
Multiomics approach – From genetics to metabolomics

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Genetic etiology research has demonstrated an unprecedented level of heterogeneity of IBD with more than 160 identified disease associated variants and loci. However, intense modeling of the genetic architecture failed to establish a direct relationship between particular patterns of genetic susceptibility and certain (sub)phenotypes. This included attempts to use genetic susceptibility to predict drug responses ex ante.

Systems biology is a powerful approach to understand complex pathophysiologies in cell cultures and other in vitro systems. The introduction of a perturbation by neutralizing or adding key factors to synchronize pathophysiology is an essential element to delineate single factors of importance in complex pathophysiologies. In this setting time series experiments around a perturbation are conducted in which OMICS datasets are obtained in short intervals.

The use of biologics in IBD has similarities to the perturbation approach in cell culture systems. The neutralization of a key cytokine (e.g. TNF, IL23 or IL6) will allow to dissect disease pathophysiology into single processes and to use this knowledge to build systems medicine models of disease. Key insights that have been derived by these clinical experiments include the relationship between cytokine driven chronic inflammation and metabolic changes that predispose to diabetes or vascular disease, respectively.

At present, systems modeling of disease is based only on selected datasets. A full multiomics approach that comprises functional genomics from several compartments, the microbiome, the genetics of the patients, epigenome modifications and an unbiased approach to the metabolome which all would have to be assessed at several time points in the context of an intervention meets significant technical difficulties that are caused by the extreme size and complexity of these multidimensional, BIG datasets.
Immunopathogenesis of inflammatory bowel diseases

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Inflammatory bowel diseases (IBD), such as Crohn’s disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory disorders of the gastrointestinal tract that are characterized by an uncontrolled mucosal immune reaction. Studies on the pathogenesis of IBD in recent years have implicated an important role of a pathologic activation of the mucosal immune system in a genetically susceptible host. In particular, an activation of mucosal dendritic cells, macrophages and T lymphocytes have been described. Moreover, innate lymphoid cells have been suggested to contribute to IBD pathogenesis. Aberrant and excessive production of inflammatory cytokines by mucosal immune cells has been implicated as a critical factor in perpetuating intestinal inflammation in the immunopathogenesis of IBD. In particular, tumor necrosis factor (TNF) was identified as a major mediator of the inflammatory process, eliciting a wide spectrum of immunostimulatory effects. Its functional relevance is highlighted by the clinical efficacy of neutralizing antibodies to TNF, which have become an integral part of therapeutic regimens to induce and maintain remission in IBD patients. In addition to TNF, other cytokines such as IL-6 and IL-23 have been identified as potential targets for therapy in IBD. Cytokines and other mediators finally activate gut resident cells and cause various complications of the diseases such as fibrosis, stenosis and IBD-associated cancer. This presentation will highlight recent research on the immunopathogenesis of IBD as a rationale for optimized targeted therapies.
The search for causative environmental factors in IBD

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IBD has become a „prototype disease” for chronic autoinflammatory disorders with a polygenic background and important sequentially multi-facetted, environmental-trigger components. Environmental factors contribute both to pathogenesis and disease flares.

Thus, IBD is a disease par excellence to study the interactions between host genetics, environmental factors (such as infections or smoking) and „in-vironmental” factors – for example, our intestinal microbiome. Longitudinal intercurrent events, including the impact of long-term medication on disease progression or stabilization can exemplarily be studied in this disease group.

Whilst alterations in the human genome coding relevant variant protein products have most likely not emerged significantly over the last 50 years, the incidence of Crohn’s disease (CD) and ulcerative colitis (UC) has dramatically increased in Western countries (Juillerat, 2008; Molodecky, 2012) and more recently in the Asian-Pacific area (Ng, 2013). A current concept indicates that „Western lifestyle factors”, such as improved hygiene, trigger chronic intestinal inflammation or disease flares in a genetically-susceptible host (Ng, 2013; Ananthakrishnan, 2013). This hypothesis is also applied to allergic and autoimmune diseases, but the underlying mechanisms are controversial. To understand the disease pathogenesis as well as triggers for flares or determinants of disease courses we must work on en(in)viro-nmental factors. To deconvolute the multidimensional host-genetics → environment → microbiota complexity of human IBD, it is vital to study clinical material that interrogates these different factors across the trajectory of disease development, progression, relapse, and/or postoperative recurrence. This is possible with longitudinal cohort studies that combine epidemiological approaches with cutting-edge genetic, epigenetic, environmental, and microbiome composition and function data such as the Swiss IBD Cohort Study (SIBDCS). As environmental conditions – in contrast to genetic risk factors – can be influenced, knowledge on those risk factors becomes crucial to modulate disease incidence, disease course or clinical presentation. It is obvious that prevention of environmentally triggered disease flares would be a goal most relevant for IBD patients.

An increased prevalence of IBD in urban environment has been documented in Switzerland by the SIBDCS (Juillerat, 2008). Unfortunately clear data on distinct environmental factors are limited. Several studies have attempted to identify such factors, however, only a few have been validated (Molodecky, 2010). The best investigated environmental factor in IBD identified in cohort analyses is smoking. Active smoking clearly worsens the disease course for CD patients (Cosnes, 2004). Other environmental factors that have been associated with clinical presentation or risk of inflammatory flares as well as increased incidence are diet and food additives (Cosnes, 2010). The so-called „Hygiene Hypothesis” suggests that increased hygiene in childhood associated with reduced exposure to pathogens may leave the mucosal immune system insufficiently trained and thus prone to uncontrolled inflammation (Ng, 2013;
Hafner, 2008; Klement, 2008). Oral contraceptives and non-steroidal anti-inflammatory drugs (NSAIDs) are the two main classes of frequently taken drugs that have been attributed to have potential to cause flares of the disease (Carbonnel, 2009; Cosnes, 1999; Danese, 2004).

What is likely to be the connection between the genetic susceptibility and the environmental triggers? There is broad evidence for a critical role of the commensal enteric microbiome as a modulator of immunologic responses relevant during onset and chronification of IBD (Round, 2009).
Does food trigger inflammation?

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While there has been substantial progress in identifying genetic risk factors of complex genetic diseases such as inflammatory bowel diseases (IBD) or rheumatoid arthritis (RA), our knowledge about the environmental factors as major disease drivers remains significantly underrepresented. There is indeed increasing evidence that ingested diet-borne components are critically involved in the pathogenesis of disorders including IBD, atherosclerosis, and type-2-diabetes. In a sense nutritional components can induce short- and long-term effects on the composition of the gut microbiota. A typical Western diet (enriched in fat, phosphatidylcholine, and L-carnitine) promotes inflammation and atherosclerosis through specific fatty acids and degradation products such as trimethylamine-N-oxide. On the other hand there are dietary factors such as carbazoles or tryptophan-enriched protein conferring anti-inflammatory properties. Such factors may exert direct effects on host targets such as the aryl hydrocarbon receptors. Alternatively these effects can be triggered by microbial products, and the microbiota and its metabolic machinery produces a myriad of metabolites that serve as important mediators in the interplay between diet, microbiota, and the host. Short-chain fatty acids (SCFA) evolved as important modulators between the food-borne soluble fiber, the microbiota and the immune and metabolic pathways. SCFA exert their effects through different mechanisms including specific G-protein coupled receptors, modulation of epithelial oxygen consumption, and epigenetic mechanisms. By identifying and expanding our knowledge about the underlying mechanisms of the interplay of diet, immunity, and the microbiome, we might develop novel food-based approaches to prevent or treat many major diseases. There is increasing scientific evidence to support the adage “we are what we eat” – a process that begins in early life.
Session VI

IBD – diagnosis and therapy
**Role of MRI in IBD patient management**

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Conventional colonoscopy combined by histological examination, represents the standard for the evaluation of ileocolonic disease and is usually the first choice examination for the evaluation of patients with suspected or established IBD. However it is now increasingly recognized that information provided by colonoscopy is limited to mucosal alterations. The technique is unable to estimate the depth of involvement of intestinal lesions, and does not provide information on the presence of extraluminal complications such as abscesses or fistula, or the length and characteristics of a stenotic lesion that cannot be passed with the endoscope.

Recent technological advances in the area of magnetic resonance (MR), along with optimization on the use of luminal and intravenous contrast greatly improved spatial and tissue resolution of MR. Recent studies have shown a high accuracy of MR to determine the presence of inflammatory activity, and its severity with high correlation with endoscopic findings, and the superiority of MR for assessment of penetrating and stenosing complications. MR has a high impact on patient management that is superior to endoscopy in patients having disease complications, and has been established as the technique of choice to assess long term damage progression.

At the time of disease diagnosis endoscopy has a primary role, and MRI is necessary for establishing disease extension in the small bowel and exclude complications. In established disease MR could be the first choice examination. However, for examination of small bowel lesions capsule endoscopy has a higher diagnostic yield than MR, and in patients with suspected activity and normal MR endoscopy should be considered to exclude the presence of mid lesions.

MR has been shown to have a high accuracy and reliability in assessing therapeutic responses in Crohn’s disease, and implementation of the technique in clinical trials may help in selecting an adequate population, and in performing repeated assessments. Finally, the recent development of the Léman index for assessment of bowel damage and progression over time makes MR an essential part in the management of IBD patients.
Corticosteroids and 5-Aminosalicylate derivatives (5-ASAs) have been successfully used for the treatment of IBD for more than half a century and play still today a key role in the treatment of IBD despite better understanding of the etiopathogenesis of IBD and numerous recently emerging novel drugs. Treatment with systemic corticosteroids provides the most rapid and effective immediate response of all currently licensed IBD medications in patients with moderate to severe ulcerative colitis (UC) and Crohn’s disease (CD). However long-term steroid treatment causes severe, sometimes irreversible and not acceptable side effects limiting their repeated or long-term use. Systemic corticosteroids are not indicated for maintenance of remission. In patients with steroid-dependent or steroid-refractory IBD alternative treatment strategies are needed. Alternative strategies may encompass treatment with topically acting corticosteroids and aminosalicylates besides numerous other therapeutic options.

5-ASAs represent the standard of care in mild to moderate UC and remain a fundamental strategy for the induction and maintenance therapy in mild to moderate UC. Topical 5-ASA is the most efficacious treatment in distal UC. Oral 5-ASAs have been shown to be highly effective in inducing and maintaining remission in mild to moderate UC with extensive and also left-sided involvement. Interestingly, combined treatment with oral and rectal application of 5-ASA improves the therapeutic responses in both distal and extended UC. New 5-ASA dosing schedules in UC with once daily dosing have demonstrated that patients’ adherence to 5-ASA therapy can be improved significantly. The role of 5-ASAs in CD is less clear. There seems to be a slight benefit in a subgroup of patients with mild CD and also in the postoperative setting in order to prevent recurrence of disease following surgical therapy of CD. A number of unsolved questions remain to be addressed in the future regarding optimal use of 5-ASA’s in IBD.

Locally acting corticosteroids have been developed to make advantage of the significant therapeutic efficacy of corticosteroids without their harmful adverse effects. Controlled ileal release forms of budesonide play a significant role in the treatment of mild to moderate ileocaecal CD and budesonide foam and enemas in mild to moderate distal UC. The recently licensed budesonide MMX formulation has demonstrated significant clinical benefits in patients with mild to moderate extensive UC without frightening side effects. Some other locally acting corticosteroid formulations like beclomethasone diproprionate or betamethasone are also used in some countries.
Are immunosuppressants becoming obsolete?

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Here we define immunosuppressants as the „classic tools“ in IBD therapy including in particular thiopurines and methotrexate. Historically, in the 1950s the introduction of simple, old-fashioned steroids resulted in a significant drop in mortality and hence offered for the first time a real therapeutic option for IBD patients. However, as we are all aware of, steroids are no option for maintenance of remission. An early study by O’Donoghue et al. provided solid evidence underlying the role of azathioprine in maintenance of remission by demonstrating that withdrawing azathioprine in patients with clinical remission results in a significantly higher rate of relapse as compared to the group where azathioprine was continued [1]. In a similar study design these data were confirmed by Vilien et al. [2]. In line, the study by Lémann et al. included patients who had been in clinical remission for 5 years, here therapy was continued in 40 patients and 43 patients received placebo [3]. The primary endpoint was a flare after 18 months, 8% of the thiopurine group and 21% of the placebo group met this endpoint. This effect could equally be shown in the pediatric cohort [4]. In a recent trial from Spain 131 patients with newly diagnosed Crohn’s disease were randomized to receive either azathioprine or placebo [5]. No adjustment to risk factors allowing for prediction of a complicated disease course was performed. After 76 weeks no significant effect of azathioprine could be demonstrated, however there are some points to consider that might in the end indicate that the power for the group of interest was not sufficient to demonstrate superiority of azathioprine. More confusingly, the RAPID-trial from the GETAID group, including patients with predictors for a more severe disease course, did not show a significant effect after 3 years [6]. However, already after 11 months in the trial over 60% of patients received azathioprine in the conventional placebo arm. Thus the endpoint at 3 years appears to be rather difficult. Last, the recently published registry on 220 patients who were after one year in clinical remission and were followed for ten years under azathioprine demonstrate the power of azathioprine in the maintenance of remission [7]. Will this be of impact when more defined targets will be approved or will the sole role of the classic immunosuppressants be the reduction of drug antibodies? These considerations are indicating that we are, and will be even more when additional options are available, in desperate need of markers guiding our decisions individually for each patient.
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Anti-TNF and anti-integrin therapies: Still second line?

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The advent of biological has revolutionized the management of IBD. However, only recently has the rate of serious complications leading to surgery begun to drop. Most likely, this has to do with suboptimal timing of the introduction of potent agents that have the capacity to heal the inflamed gut.

Despite strong evidence in favor of earlier use of immunomodulatory agents, most physicians remain reluctant to initiate them timely. The main reasons are local guidelines that lag behind existing evidence, fear of toxicity and the higher cost of biologic treatment.

Increasingly, however, the GI community has adopted the ‘top-down’ treatment concept for certain categories of patients. There is little controversy that patients with perianal fistulization, severe extraintestinal manifestations and extensive small bowel disease need aggressive therapy up front. To extend the ‘top-down’ indication to moderate-severe phenotypes without these extreme manifestations is currently still a matter of debate.

Efforts are being made to identify patients that have a high likelihood of severe and progressive disease. Relevant predictors not only include phenotypic characteristics, but potentially also genetic markers, proteomic profiles and perhaps even microbiome subtypes that could all be helpful to individualize treatment.

Whether the existing knowledge related to anti-TNF drugs is equally relevant for anti-integrin antibodies such as vedolizumab and ertolizumab remains to be seen. It has not been reported, so far, to what extent vedolizumab heals the mucosa and reduces fistula formation and need for bowel resection. Likewise there are no data demonstrating superior efficacy in early disease.

Undoubtedly emerging data will allow a more personalized management of IBD, not only to facilitate the most optimal drug selection for patients but also to improve the timing of these interventions so that the natural history can be improved drastically.
Session VII

Precision medicine in IBD
Proper use of IBD drugs during pregnancy

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Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), are chronic, relapsing conditions. IBD typically arises at a young age, and approximately 25% of IBD women will become pregnant after diagnosis. While several decades ago most physicians would discourage pregnancy in IBD patients because of fear of adverse outcomes, it has currently been generally accepted that IBD or its treatment is no reason to make patients refrain from fulfilling their reproductive wish. The most important risk factor for adverse pregnancy outcomes however, is thought to be the presence of disease activity during pregnancy. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery, thromboembolic events, emergency caesarean section and low birth weight, whereas the majority of pregnancies in women with quiescent IBD will be uncomplicated. This indicates the necessity of maintaining remission with the continuation of medication. Knowledge on the effects of IBD drugs on the child in utero is therefore of utmost importance to council IBD patients with a pregnancy wish.
Early surgery for Crohn’s disease

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Crohn’s disease (CD) is a chronic and progressive disease characterized by the presence of inflammation in different segments of the digestive tract, resulting in damages of the entire wall. Untreated or treated inappropriately, this eventually might result in strictureing and/or penetrating complications. Traditionally, the first line of treatment is medical, and surgery reserved for those who failed medical therapy. Insights have changed over the past years. Symptomatic control medically does not rule out disease activity, and the results of targeted therapy must be monitored in order to avoid complications of the disease. Particularly patients with penetrating disease might end up with unnecessarily extensive resections of surrounding healthy organs that are affected by inadequately treated or responding penetrating disease. Likewise, patients with inactive strictures are not going to respond to medical therapy. Well-indicated and minimal invasive surgery can be considered as an alternative to long-term medical therapy particularly if timely surgery involves only relatively small segments of bowel without compromise of quality of life. Examples are all segmental small and large bowel resections, larger colon resections were restoration of continuity and seton drainage of perianal sepsis. Under all circumstances, decision making must be done in multidisciplinary teams.
Personalisation in the treatment of IBD reveals a distinct biology of clinical outcome in immune-mediated disease?

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Western medicine has developed by classifying disease into defined diagnostic categories, and modern genetics and genomics has largely been occupied trying to uncover the genetic variants that drive their development. Even within a specific diagnostic category, however, the clinical course a disease takes can vary greatly between individuals. Thus to a patient with immune-mediated disease, for example, long-term outcome can be far more important than the specific diagnosis they are given.

To investigate what controlled long-term patient outcome we recruited patients with Crohn’s disease, ulcerative colitis, ANCA-associated vasculitis and SLE, at diagnosis. We then performed a comprehensive RNA expression analysis of separated leucocyte subsets and correlated this with prospective clinical follow-up data over a median of 6 years. We found a CD8 T cell transcription signature that predicts outcome, but is not associated with diagnosis, in these important immune-mediated diseases. A candidate gene study based on pathways identified by this signature in Crohn’s disease revealed a novel pathway driven by FOXO3 that regulates inflammation and is associated with long-term outcome, but not diagnosis, in a number of conditions.

This presentation will explore new data extending this work that defines a clinically useful prognostic biomarker in IBD, but also addresses the specific immunological mechanisms driving long-term outcome in immune-mediated disease, and the genetics that underpins this. Evidence will be presented suggesting that the biology underlying long-term disease outcome, or prognosis, is distinct from that driving specific diagnosis, and represent an under-investigated but clinically relevant aspect of disease pathogenesis.
Emerging therapies for inflammatory bowel diseases

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Abbreviations:
CD, Crohn’s disease; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus Kinase; UC, ulcerative colitis

The past decade has seen important advances in the management of the chronic inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis (UC). Refinement of the role of TNF-antagonists and combination therapy, recognition that interference with lymphocyte trafficking is a highly effective treatment strategy, and the need to treat high risk patients early in the course of the disease are fundamental concepts for future algorithms. New therapies that will lead our way forward include novel integrin inhibitors, ozanomod, ustekinumab, and the JAK-STAT inhibitors.

Vedolizumab a monoclonal antibody directed towards the α4β7 integrin, has demonstrated efficacy for induction and maintenance of clinical remission in both UC and CD. Etrolizumab a monoclonal directed towards the beta-7 integrin and PF-00547659, an anti-MadCam antibody have demonstrated promising results in Phase II UC studies.

Ozanamod is an oral, sphingosine 1-phosphate (S1P) receptor agonist that blocks lymphocyte migration from peripheral lymph nodes to the gut. A Phase II study, in patients with moderate to severely active UC displayed benefit of therapy.

Ustekinumab is a monoclonal antibody directed against the shared p40 subunit of IL-12 and IL-23 41,43,44,57. The results of large Phase III studies of this agent have recently reported positive results.
Janus kinase inhibitors reduce downstream production of pro-inflammatory TH1 cytokines. A Phase III program of Tofacitinib in patients with treatment resistant UC demonstrated positive results.

In summary multiple new therapies are now available for the treatment of IBD. Ultimately comparative effectiveness studies will be required to determine their place in treatment algorithms.
Session VIII

IBD – environmental factors
The mammalian intestinal tract harbours a complex microbial ecosystem, which is acquired after birth. Recent work suggests that the host together with the microbes forms a functional symbiosis in health and disease, the “intestinal metaorganism”. More than 1000 different bacterial species are estimated to be present in the human gastrointestinal tract, with a density of 1011 bacterial cells per gram wet weight in the distal large bowel contents. The intestinal ecosystem builds the first line of defense against enteric pathogenic infections and toxic or otherwise noxious agents (e.g. from food) and is beneficial for immunological and metabolic homeostasis. Large-scale human microbiome sequencing efforts have demonstrated remarkable interindividual differences, which are systematically influenced by a number of factors including diet, host genetics and behavior. Several studies including our own nevertheless describe the existence a limited number of realized overarching composition principles, enterotypes or -gradients, suggesting that a distinct number of optimal metabolic states may represent a feature of host-microbial physiology. Human chronic inflammatory bowel disease (IBD) is a prototype of chronic immune-mediated diseases, where a strong link to an altered gut microbiome has been provided. The diseases usually become manifest between the 2nd and 4th decade of life and are associated with a significant degree of long-term disability. Recent advances have been made in the description of genetic risk factors and formal pathophysiology (e.g. the description of inflammatory signal transduction), yet the complex questions why the IBD manifests at a specific time and how the disease is perpetuating over time in a given individual are completely unresolved, yet several observations have been made indicating an involvement of a disturbed host-microbe crosstalk and an influence of dietary factors.

Here, I will review the recent state of literature and discuss evidence how microbial patterns might be linked to manifestation and progression of IBD. The hypothesis that microbial and nutritional challenges might be among the main causative factors of disease manifestation in genetically susceptible individuals clearly connotes a potential therapeutic and/or preventive exploitation in IBD and beyond. Yet, we have to keep in mind that the plasticity of the microbiome is also prone to secondary changes due to inflammation (hen and egg phenomenon). Thus, we have to understand underlying principles of co-metabolism rather than simple taxonomical fingerprints. If we are able to disentangle early disturbances of the complex symbiotic network in the gut, the knowledge indeed may lead us to completely novel interventions and preventive measures for this debilitating group of diseases.
Any future for fecal transplant as treatment strategy for IBD?

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The intestinal microbiota is essential for maintaining human health, defending against intestinal pathogens and for a normal function of the intestinal immune system. Alterations of the intestinal microbiota, also termed dysbiosis, seem to play an important role in the pathogenesis of inflammatory bowel diseases (IBD). Fecal microbiota transplantation (FMT) aims on correcting these alterations by delivering fecal microorganisms from a healthy person to the intestines of a patient. Up to now, recurrent Clostridium difficile infection is the only indication for FMT supported by solid scientific evidence. Several small clinical trials and ongoing studies are investigating FMT also in different forms of inflammatory bowel diseases including chronic active ulcerative colitis (UC), Crohn’s disease (CD), pouchitis and C. difficile superinfection in IBD. So far most studies exist for chronic active UC, including two randomed controlled trials, one of those showed a significant effect of FMT in improving disease activity compared to the control group. An effect of FMT in chronic active UC is also supported by some of the uncontrolled trials. In published UC studies remission rates to FMT vary between 0–30% and response rates between 20 and 60%. In CD there are less and only uncontrolled trails. The largest two case series reported a modest effectiveness of FMT in CD. In C. difficile superinfections in IBD patients, FMT seems to eradicate C. difficile with variable effects on the underlying IBD. Exacerbations of IBD after FMT have been reported for all indications. FMT in all IBD is still an experimental therapy and should be performed only in clinical trials. As there are no large systematic methodological investigations, several questions about techniques, donor screening and selection and especially long term safety issues remain.
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POSTER ABSTRACTS

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Comorbidities in alcoholic liver cirrhosis

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**Introduction:** Alcoholic liver disease is one of the most serious complications of alcohol abuse, but other organs may also be affected by long-term alcohol dependence. Patients with alcoholic liver cirrhosis (ALC) frequently suffer from various comorbid conditions. These comorbidities have a significant impact on cirrhosis progression, low rate of transplantation and mortality and are therefore clinically important. Comorbid medical conditions that either are a direct complication of alcoholism (e.g., alcoholic cardiomyopathy, various neurological diseases, malnutrition, osteopenia) or are commonly found in alcoholic patients (e.g., coronary artery disease (CAD), hepatitis C virus (HCV) infection, hepatocellular carcinoma (HCC)) are discussed in academic papers.

The aim of this study was to evaluate the prevalence of comorbidities in patients with ALC.

**Methods:** A total among of 164 adults with ALC (97 men, 67 women, median age 51 [28–79] years, Child-Pugh class A – 15.9%, B – 47.8%, C – 36.3%) hospitalized at a gastroenterology clinic between September 2011 and February 2014 were included in the study retrospectively. Comorbidities were diagnosed using standardized investigations. Clinical data were collected from the medical chart.

**Results:** The most frequent comorbidities were: malnutrition (114/89%), gastro-duodenal ulcer (62/37.8%), osteopenia (52/31.7%), peripheral neuropathy (37/22.6%) and HCV infection (25/15.2%). The prevalence of alcoholic cardiomyopathy was 15/9.1%. Chronic kidney disease (14/8.5%), CAD (12/7.3%), arterial hypertension (10/6.1%), chronic obstructive pulmonary disease (9/5.5%), HBV infection (7/4.3%) occurred rarely. Cases of neurological diseases, Korsakoff’s psychosis, chronic cerebral dysfunction, alcoholic cerebellar degeneration, chronic pancreatitis were occasional. HCC was not found. Direct complication of alcohol abuse occurred significantly more frequently (P < 0.001), which was predictable.

**Discussion/Conclusion:** Comorbidities are widespread among patients with ALC. Their identification and treatment are important in improving outcomes in this patient group.
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 $\alpha$ was 0.88, item-total correlations were good and there was no ceiling or flooring 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 $\alpha = 0.84$); 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.
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 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.
Dendritic cells, TGF-β1 and insulin-like growth factor II mRNA binding protein 3 – „Heroes or villains” in IBD pathology

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Introduction: Ulcerative colitis (UC) and non-specific colitis (NSC) are inflammatory disorders with some common genetic, immunological and environmental factors involved in the pathogenesis. One of mechanisms involve in the processes is transforming growth factor-β1 (TGF-β1), a cytokine, that is produced by multiple cell types and targets both immune and nonimmune cells. Our previous study shows that other markers like insulin-like growth factor II mRNA binding protein 3 (IMP3) was correlated with disease aggressiveness and progression.

Methods: The immunohistochemical expression of TGF-β1, IMP3 and density of CD1a, and CD83-positive dendritic cells was evaluated in 28 patients (13 with UC and 15 NSC). The results were compared with clinical and pathological parameters of investigated patients.

Results: Our results revealed expression of TGF-β1 in 53.8% of UC and 33.3% of NSC (p = 0.028), and IMP3 expression in 30.8% of UC patients, while none of NSC showed positive expression. The IMP3 expression in UC specimens correlated with low CD1a+ and low CD83+ DCs infiltration (p = 0.05 and p = 0.041, resp.). In addition, the expression of IMP3 were higher in specimens with TGF-β1 expression in both groups.

Finally, patients with more histologically progressive UC had intense expression of IMP3 and TGF-β1 and low infiltration with CD1a+ and low CD83+ DCs.

Discussion/Conclusion: Our results suggest that infiltration with DCs and expression of IMP3 and TGF-β1 may be of great importance for the prognosis in ulcerative colitis and non-specific colitis.
The peculiarities of colonic microbiota in patients with NSAID-associated liver injury

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Background and Aims: The peculiarities of colonic microbiota in patients with NSAID-associated liver injury haven’t been studied before. The aim of our work was to evaluate the quantitative and qualitative changes patients with prolonged use of NSAIDs and NSAID-associated liver injury.

Methods: We observed 94 patients with osteoarthritis who used NSAIDs for more than 1 month. The mean age was 64.1 ± 0.79. For all of them gastroscopy with further morphological examination, H. pylori detection, laboratory examination (complete blood count (CBC), ALT, AST, bilirubin, GGT, AP) were performed. The fecal microflora has been analyzed by bacteriological culture methods. Normal distribution of studied parameter for each sampling was checked using Shapiro-Wilka’s criteria.

Results: The mean levels of ALT, AST, and GGT were significantly elevated in patients who used NSAIDs compared to the control group. H. pylori was detected in 58% of patients. Changes in colonic microbiota were observed in all patients who used NSAIDs for more than 1 month. The colonization of Escherichia coli was (1.34 ± 0.30) x 10⁶, that in 32 times exceeded the indicator in control group (p < 0.001). The colonization of Enterococcus was increased in 700 times (p < 0.01); the levels of Bifidobacterium and Lactobacillus were decreased in 100 times (p < 0.001) and 1000 times (p < 0.01) accordingly. In H. pylori-positive patients the increase of Candida in 8 times was observed. With age the changes in obligate microflora were observed: the concentration of Bifidobacterium in patients up to 60 years was (11.0 ± 2.3) x 10⁶, in patients 61–70 years – (8.7 ± 2.2) x 10⁶, in patients more than 70 years – (1.8 ± 0.3) x 10⁵.

Conclusions: The inclusion of multiprobiotic in the general scheme of treatment of NSAIDs-gastropathies is petrogenetically approved as with age the suppression of motor function of the intestine is observed. The long-term use of NSAIDs leads to quantitative and qualitative changes of colonic microbiota and elevates the levels of ALT, AST and GGT.
De novo IBD as one of significant risk factors for PSC recurrence after liver transplantation

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic liver disorder and one of the most common indications for orthotopic liver transplantation (OLT). Recurrent form of PSC (rPSC) often appears in patients after OLT and may eventually lead to graft loss and liver re-transplantation (re-OLT). PSC is often accompanied by inflammatory bowel disease (IBD) which can appear both before and after OLT.

Methods: We retrospectively analyzed medical records of 115 patients transplanted for PSC. Only patients with a proper record of pre-OLT (≤ 12 months) colonoscopy and those monitored for a time period of ≥ 60 months post-OLT were included. Input data were analyzed using JMP statistical software. Student’s t-test, Fisher’s exact test and nominal logistic regression were used to assess the data. A p-value < 0.05 was considered as statistically significant.

Results: After applying inclusion criteria, we analyzed a cohort of 47 patients. 31 were male, 16 female, with median age of 36 (range 15–68) and median follow-up 122 months (range 60–249) after OLT. In 21/47 (44.7%) patients, rPSC was diagnosed during the follow-up. Two patients underwent re-OLT (after 103 and 116 months respectively, both for rPSC). Presence of de novo IBD (p = 0.0002; OR = 27.50, 95% CI: 3.13–241.94) and OLT for overlap with autoimmune hepatitis (p = 0.0133) were significantly associated with rPSC. Presence of HLA-DRB1*04 in the recipient was identified as protective factor for rPSC (p = 0.0287). In case of de novo IBD, statistical significance was further confirmed by nominal logistic regression analysis (p = 0.0094; OR = 22.00, 95% CI: 2.04–591.60).

Discussion/Conclusion: Recurrent PSC is an important clinical entity with high prevalence in patients after OLT. De novo IBD is a novel significant risk factor associated with rPSC.
**PSC patients have different microbiota composition as compared to UC**

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**Introduction:** Primary sclerosing cholangitis (PSC) is a progressive disease of the biliary tree characterized by inflammation, fibrosis and stenoses. Inflammatory bowel disease (IBD) in patients with primary sclerosing cholangitis (PSC – IBD) is considered to be a distinct phenotype of IBD where microbiota most likely have a substantial role. Our aim was to compare the microbiota composition in PSC and PSC – IBD groups with ulcerative colitis (UC) and healthy controls.

**Methods:** We recruited 96 individuals – 32 healthy controls, 32 UC patients, 24 PSC-IBD patients and 8 PSC patients without IBD. Fecal microbiota composition was analyzed by sequencing of variable V3 and V4 region of 16S rRNA gene using Illumina MiSeq™ platform. Library preparation, template preparation and template sequencing was performed according to manufacturer’s protocols. Obtained data were filtered by quality and length and processed for alpha and beta diversity analyses using QIIME software package.

**Results:** We found considerable inter-individual variability in microbial community composition within all experimental groups. Nevertheless, PSC was associated with distinct gut microbial signature as compared to other groups. Verrucomicrobiales genus Akkermansia was specifically overrepresented in PSC group and genus Streptococcus from the order Lactobacillales was significantly more abundant in both PSC and PSC-IBD groups as compared either to UC or controls. Moreover, the overall richness of microbial composition varied among groups.

**Discussion/Conclusion:** We showed that PSC patients have microbiota composition distinct from PSC – IBD and UC. Further analysis and correlation with clinical data are needed to evaluate the clinical significance of these findings.
Cardiovascular risk factors in young patients with inflammatory bowel disease associating non-alcoholic steatohepatitis

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Developed in young people, inflammatory bowel disease may cause various cardiovascular manifestations, underdiagnosed, masked by digestive symptoms, but affecting the quality of life. Sometimes, association of steatohepatitis may also increase cardiovascular events risk.

**Aim:** The assessment of cardiovascular risk factors in young patients with IBD associating NASH.

**Patients and Methods:** The study was conducted on 12 patients, aged between 20–40 years, diagnosed with ulcerative colitis and non-alcoholic steatohepatitis, who presented extradigestive manifestations such as cardiovascular events. Risk factors induced by IBD itself and steatohepatitis were assessed, in order to determine their implication in cardiovascular complications occurrence. The research pursued clinical and laboratory explorations, both for digestive tract and liver, as well as for cardiac-circulatory system.

**Results:** IBD and steatohepatitis diagnosis was confirmed in particular by paraclinical (endoscopy, ultrasound, biopsy) and clinical data (bowel disorders, hepatomegaly, hepatic cytolysis); cardiac manifestations were evaluated by clinical data, electrocardiogram, ultrasound and radiological investigations.

Induction parameters for cardiac events in IBD and NASH context, were: anemia, hydroelectrolytic disorders (potassium-sodium), dyslipidemia, autoimmune inflammation, intestinal hemorrhage, abdominal pain, anxiety, hepatic cytolysis, oxidative stress. Recorded cardiac manifestations were: cardiac rhythm disorders (predominantly with high frequency), ischemic modifications, variations of blood pressure, vascular atheroma (carotid). Arrhythmias were present in 10 patients, variations of blood pressure-hypotension in 8, hypertension in 4 patients, myocardial ischemia in 3 (documented by ECG), carotid atheroma plaque in 2 patients.

**Conclusions:**
1. Association of inflammatory bowel disease with non-alcoholic steatohepatitis pathology can interrelate, inducing extradigestive complications in youngs.
2. Cardiac risk is determined by multiple factors association: electrolytes disorders, dyslipidemia, increased level of oxidative-stress enzymes, psychological stress, immune abnormalities.
3. Dysrhythmias, blood-pressure disturbances, cardiac lesion may be present in acute inflammatory process but also in IBD long-term evolution.
4. IBD and NASH monitoring and treatment represent prevention and control measures of present or future cardiovascular risk.
The importance of oxidative stress assessment in patients with inflammatory bowel disease associating non-alcoholic steatohepatitis

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In the evolution of inflammatory bowel diseases, non-alcoholic steatohepatitis can be present, as complication or as associated disease. Disturbances of lipid peroxidation balance and the occurrence of oxygen radicals may influence both the evolution and therapy of pathological conditions, inducing the necessity to determine oxidative specific biomarkers.

Aim: Determination of oxidative stress level in patients with IBD associating NASH, in context of pathogenic and therapeutic implications.

Patients and Methods: The study was conducted on a group of 11 patients, aged between 24 and 44 years, presenting ulcerative colitis associated with non-alcoholic steatohepatitis. There were determined oxidative stress enzymes (malondialdehyde, nitric oxide) and the level of antioxidative enzymes (glutathion peroxidase and superoxide dismutase), concomitant with clinical, biochemical, imagistic explorations, regarding the stage of inflammatory disease and liver steatosis.

Results: Markers of oxidative status were modified in all patients, proofing acceleration of lipid peroxidation, with an increased level of oxidative enzymes and a decreasing of antioxidant enzymes. Perturbations of oxidant-antioxidant balance are influenced and also influence the immune aggression at gut and hepatic level, requiring assessment, control measures and adequate dietary treatment. Monoxygenase enzyme of the P450 II D6 (CYP 2D6) cytochrome, as marker of metabolic aggression illustrate immune imbalance. These conditions may be influenced by immunosuppressive therapy.

Conclusions:
1. Biomarkers of oxidative stress are important in assessing ulcerative colitis associated with NASH.
2. Determination of malondialdehyde, nitric oxide as oxidative enzymes, as well as glutathion peroxidase and superoxide dismutase as antioxidative enzymes allows evaluating and calculating oxidative stress level and estimating the imbalance.
3. Interrelation between inflammatory lesions, hepatic conditions and an increased oxidative stress level worsen the evolution and complications both of inflammatory bowel disease, as well as of NASH.
4. Demonstration of oxidative stress biomarkers perturbations allows an adequate involvement and control of diet and immunosuppressive therapy.
Circulating bone marrow derived CD45-/CD34+/CD133+/VEGF+ endothelial progenitor cells in adults with Crohn’s disease

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Introduction: Circulating endothelial progenitor cells (EPCs) are bone marrow-derived stem cells able to migrate to sites of damaged endothelium and differentiate into endothelial cells in response to tissue damage. Altered EPC level and function have been described in various inflammatory diseases and have been shown to augment vasculogenesis in murine models. EPCs have not been previously studied in the context of Crohn’s disease (CD).

Methods: CD patients and healthy controls were recruited. Disease activity was assessed by CDAI. Peripheral blood mononuclear cells were isolated and CD45-/CD34+/CD133+/VEGF+ EPC numbers evaluated by FACS analysis using phycoerythrin anti-CD34, allophycocyanin anti-VEGF receptor-2, FITC-anti CD 133 and anti-CD45 markers.

Results: Thirty two CD patients and 51 controls were recruited (including 19 (59.4%) and 23 (45%) males (p = 0.26), aged 34.8 ± 14.9 and 43.3 ± 18.5 years (p = 0.64), in cases and controls, respectively). Mean CDAI was 147 ± 97, disease duration was 12.7 ± 11.1 years and 28 (87.5%) were receiving biologics for a mean duration of 21.7 ± 16.8 months. The mean level of peripheral EPCs in CD patients was 0.050 ± 0.086 and 0.007 ± 0.013 in controls (p < 0.01). There was no significant correlation between EPC levels and age (r = -0.13, p = 0.47), gender (t = 0.48, p = 0.64), CDAI (r = -0.26, p = 0.15), disease duration (r = -0.04, p = 0.84), duration of treatment with biologics (r = 0.004, p = 0.99), or smoking (t = 0.74, p = 0.47).

Discussion/Conclusion: EPCs are significantly elevated in patients with CD. Further studies are needed to examine the function of EPCs and their possible role as a marker of disease severity or therapeutic response.
FACS analysis of CD34+cells
Successful pregnancies with thiopurine-allopurinol co-therapy for inflammatory bowel disease

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Introduction: Thiopurines (azathioprine [AZA] and mercaptopurine [6MP]) are an effective treatment for moderate to severe IBD and maybe used safely in pregnancy. Combining allopurinol with a lower dose of thiopurine can improve clinical efficacy and bypass some of the adverse reactions associated with thiopurine monotherapy. There are scarce data regarding allopurinol in pregnancy and it is classed by the US Food and Drug Administration (FDA) as a category C drug in pregnancy based on animal evidence of teratogenicity at high doses in mice but not in rats. There are only a few reported cases on the combined use of thiopurine and allopurinol during pregnancy. We report on a total of eleven cases where thiopurine and allopurinol co-therapy was used successfully to manage IBD during pregnancy. This represents the largest case series of thiopurine and allopurinol co-therapy for IBD in pregnancy to date.

Methods: Patients were retrospectively identified at our two hospitals in the UK and in Australia, using our local IBD databases. All pregnancies of co-therapy patients were included. TPMT activity and pre-pregnancy weight were used to calculate thiopurine dosing. Disease severity was assessed with simple colitis score for ulcerative colitis and Harvey Bradshaw Index for Crohn’s disease. Data regarding pregnancy and fetal outcomes including in-utero fetal ultrasound scans, APGAR scores, fetal birth weights and neonate checks were collected from patient notes.

Results: 11 cases identified; 8 live births, 3 pregnancies ongoing, no miscarriages
- 8 ulcerative colitis, 3 Crohn’s disease
- Average AZA dose 41 mg/day (n = 4)
- Average 6MP dose 30 mg/day (n = 7)
- Average Allopurinol dose 109 mg/day
- Length of co-therapy treatment pre-pregnancy 9.5 months (median)
- Average age at pregnancy 32 years (median)

Discussion/Conclusion: No adverse pregnancy or fetal related outcomes were detected in this case series. Maternal allopurinol use has not been shown to be related with adverse fetal outcomes despite decades of allopurinol use. Our study provides reassurance for clinicians and patients who wish to continue the thiopurine-allopurinol co-therapy combination pre-conception and during pregnancy to maintain IBD in remission.
Can fecal transplant represent a solution for inflammatory bowel disease and Clostridium difficile infection?

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Introduction: Over the past two decades has been a dramatic worldwide increase in both incidence and severity of Clostridium difficile infection (CDI). Several studies showed worse clinical outcomes in inflammatory bowel disease (IBD) patients with CDI, including longer hospital stay, higher colectomy and mortality rates than in those without CDI. The aim of our study was to evaluate the frequency of CDI in patients with IBD and to evaluate the response to treatment.

Methods: We performed a retrospective study that included 11 patients from a group of 220 IBD patients hospitalized in the Gastroenterology Department of the Clinical Emergency Hospital of Bucharest between September 2013 and September 2015 for supra infection with Clostridium difficile.

Results: The patients mean age was 42.4 years. The distribution by gender: 63.6% men and 36.4% women. The frequency of CDI in patients with IBD was 5%. Patients with ulcerative colitis were more susceptible to CDI (90.9%), than those with Crohn’s disease (9.1%).

We studied also the response to treatment. Metronidazole orally was effective in 27.2% of cases. Vancomycin orally combined with Metronidazole was effective in 63.6% of cases. Refractory CDI unresponsive to 48 hours of conventional therapy (Vancomycin + Metronidazole) appeared in 9.1% of cases. The eradication was achieved only with tigecycline and fecal microbiota transplant.

Discussion/Conclusion: Patients with ulcerative colitis are at higher risk for CDI and have a poor prognosis than those with Crohn’s disease. Average age of CDI in IBD patients significantly is lower than in general population.

In IBD patients, presenting with diarrhea, practitioners need to test for C. difficile and consider CDI with symptoms of a disease flare. Special care to rule out C. difficile should be pursued prior to escalating or starting new immunosuppressive agents. Fecal microbiota transplant, probiotics and newer antibiotics are good alternatives for refractory disease.
Isolated tongue tremor in patient with liver cirrhosis

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Background: Isolated tongue tremor is a rare focal tremor. Little is known about the etiology. Few number of cases have been reported in association with Wilson’s disease, radiosurgery, brain tumor, electrical injury, chronic alcoholism, essential tremor and side effect of a drug.

Case Report: Herein we report a patient who had an isolated tongue tremor with chronic liver disease. A 61 year-old female patient was admitted to the gastroenterology clinic because of refractory ascites, functional corruption to her speech and swallowing. She had a history of 7 year cryptogenic liver cirrhosis. There was no history of diabetes mellitus, hypertension, trauma or usage to neuroleptic drugs. Swollen abdomen and tongue tremor have been determined at her physical examination. Laboratory analysis revealed a total bilirubin of 1.08 (0.2–1) mg/dL, SGOT 47 (10–40) U/L, SGPT 33 (10–40) U/L, albumin 2.82 (3.5–5.5) g/dL, international normalized ratio 1.1, leukocytes 1.600/mm^3, hemoglobin 12.1 gr/dL, platelets 36.000/mm^3, normal electrolyte, renal and thyroid function values. On neurologic examination, low amplitude fast tremor was observed when the tongue was at rest but disappeared during optional tongue movement. Cranial and peripheral nerve functions were preserved. Motor and sensory function tests were normal. Magnetic resonance imaging of her brain and electroencephalogram were normal. She was diagnosed with isolated essential tremor of the tongue. Levels of ammonia and manganese were normal. Propranolol 40 mg/day was prescribed to break the symptoms. The tongue tremor was abated two days after onset of treatment.

Conclusion: Uncontrollable tongue movements are a few and poorly understood group of movement disorders. Various disease or condition can cause tongue tremor. To the best of our knowledge, this is the first reported case of tongue tremor in patient with liver cirrhosis. Consequently, isolated tongue tremor should be kept in mind in patients with liver cirrhosis.
**IBD phenotypes differ in gut mycobiota composition**

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**Introduction:** Inflammatory bowel disease (IBD), Crohn’s disease (CD) and ulcerative colitis (UC), is chronic idiopathic disorder of gastrointestinal tract. The inflammation in IBD is a result of an aberrant immune response to commensal microbiota in genetically susceptible individuals. Since there is a marked association of CD with gut fungal microbiota (mycobiota) we analyzed its composition in patients with CD, UC and in healthy controls.

**Methods:** We obtained stool samples from 9 CD patients, 7 UC patients and 3 healthy controls. We analyzed mycobiota composition by sequencing internal transcribed spacer (ITS2) region of fungal DNA using Illumina MiSeq. The data were processed using standard Qiime pipeline and the mycobiome alpha and beta diversity were calculated.

**Results:** Number of detected fungal OTUs was not significantly different among groups (controls = 4.7 ± 0.6, CD = 5.9 ± 3.1 and UC = 7.6 ± 2.5). Both forms of IBD increased mycobiome variability, as documented by alpha diversity in CD and UC. In IBD, Saccharomycetales and Onygenales were disrupted as compared to controls. Major qualitative differences are well documented by tight clustering pattern of all three groups, as measured by binary Jaccard metrics. This was caused mainly by appearance of Davidiellaceae family and decrease in diversity within order Saccharomyces in IBD patients.

**Discussion/Conclusion:** Our preliminary data showed that gut mycobiota has significant pattern associated with health and disease. The high variability and presence of acquired fungi suggest that disrupted gut microbial ecology in IBD support transient fungal communities. Larger groups and more experiments are needed to confirm these interesting findings and to assess their medical relevance.
Serum levels of lectin complement pathway molecules do not primarily determine the risk of bacterial infections in patients with cirrhosis

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Introduction: Bacterial infections are a frequent in cirrhosis. Lectin pathway molecules of the complement system are synthesized in the liver and have a pivotal role in the innate host defense against infectious organisms. Ficolins (FCNs) act as soluble pattern recognition molecules, while mannan-binding lectin serine proteases (MASPs) do as effector molecules in elimination of the pathogens. Low levels of the functional proteins increase the risk of various infectious diseases mostly in immune-deficient conditions but their significance has scarcely been investigated in cirrhosis related bacterial infections.

Methods: Sera of 266 patients with cirrhosis (male: 50%, alcoholics:63.9%, median age:56 years and MELD score:11), and 160 healthy subjects were assayed for the concentrations of a panel of lectin molecules (FCN-2, FCN-3 and MASP-2) by sandwich-type immunoassay. In cirrhosis, a 5-year follow-up observational study was conducted to assess a possible association between lectin levels and development of clinically significant bacterial infections (CSI) and mortality.

Results: The FCN-2, FCN-3 and MASP-2 levels were significantly lower in cirrhosis compared to healthy controls (median, 505 vs. 769 ng/ml, 7301 vs. 10797 ng/ml and 212 vs. 412 ng/ml, respectively, p < 0.001 for all) and decreased according to disease severity as rated by Child-Pugh stage. In Kaplan-Meier analysis with LogRank test, time to development of CSI was associated with low level of FCN-3 (< 4857 ng/ml, p = 0.028) but not FCN-2 (< 427 ng/ml, p = 0.068) or MASP-2 deficiency (p = 0.368). Patients with combined low level of both FCNs had a cumulative risk of an infection of 52% as compared to 31% with normal level of FCNs (p = 0.021). None of the lectin molecules, however, were associated to long-term mortality. In multivariate Cox-regression analysis, clinical factors but not the serum lectin profile remained an independent predictor of CSI. Prior episode of CSI and in a stepwise manner, the disease severity as rated by Child-Pugh stage conferred higher risk for development of CSI (HR: 2.64, 95% CI: 1.74–3.99, p < 0.001 and 2.11, 95% CI: 1.52–2.93, p < 0.001, respectively).

Discussion/Conclusion: In the present prospective study, diseases severity and prior episode of CSI but not the serum lectin profile were major determinants of the risk of CSI in cirrhosis.
The effect of the therapy with UDCA and budesonide on histological evolution of the primary biliary cirrhosis in patients with incomplete response to UDCA monotherapy

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Introduction: Aim of our study was the assessment of the effect of combined therapy (two years combined therapy with UDCA and budesonide) on histological evolution of primary biliary cirrhosis (PBC) after suboptimal response to UDCA monotherapy.

Methods: We studied 24 patients with PBC (stages I–III), with suboptimal response to UDCA monotherapy (13–15 mg/kg/day, 12 months). Due to incomplete response of this therapy, 14 patients (A group) were treated with combined therapy (UDCA 13–15 mg/kg/day and budesonide 9 mg daily divided in 3 doses) and 10 patients (B group) received increased dose of UDCA (15–20 mg/kg/day). In this comparative study we evaluated serum levels of aminotransferase, Bb, AP, liver histology, activity and fibrosis scoring (METAVIR criteria) at 6, 12 and 24 months.

Results: In both groups, clinical symptoms significant improved after 6 month (in 28.5% of cases in A group and 30% of cases in B group), in 60.7% after 12 months and 89.28% after 24 months. In B group the mean value of serum bilirubin concentration was reduced from 6.7 ± 2.5 mg%, at baseline, to 2.8 ± 1.3 mg% at 6 months and to 1.7 ± 0.7 mg% at 12 months. Aminotransferase values were reduced more quickly comparative with bilirubin and AP levels: with 44.6% at 6 months and 63.2% at 12 months. In A group, aminotransferase values reduced more slowly, but significant decrease AP after one year (p = 0.001). Inflammatory activity was significantly reduced in the combined therapy (6 cases, 42.86%) and in 2 cases (20.0%) with monotherapy. Fibrosis decreased in group A in 5 cases, but in B group only in one case. After 24 months, histological stage of disease improved only in A group (3 cases). In A group two patients presented hyperglycemia, 2 mild hirsutism and 4 osteoporosis, but in B group we observed side-effect in only one patient (diarrhea). Most of the side-effects appeared in patients with stage III PBC and only in two patients we reduced the budesonide dose.

Discussion/Conclusion: UDCA combined with budesonide improved liver histology and liver enzymes, whereas the effect of UDCA monotherapy was mainly on liver function tests. The association between UDCA and budesonide can represent an effective therapeutic option in treatment of PBS after suboptimal response to UDCA monotherapy.
Probiotics in association with UDCA in the treatment of the non-alcoholic steatohepatitis in obese patients

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Introduction: Aim of this study was to assess the effectiveness of combined therapy with UDCA and probiotics in the treatment of NASH. The efficacy of probiotic therapy in modifying liver function and her effects on hepatic steatosis or steatofibrosis were also evaluated.

Methods: We studied 42 patients with NASH and obesity. We excluded patients with viral or autoimmune hepatitis, genetic liver disease, diabetes mellitus or drug abuse. Group A was composed of 18 cases which received UDCA (13–15 mg/kg/day) in association with probiotics (which contain Lactobacillus acidophilus, Bifidobacterium infantis and Enterococcus faecium, 20 billion colony forming unit/day). The B group consist of 24 cases, treated with UDCA 13–15 mg/kg/day or combined therapy with UDCA and vitamin E (400 IU twice a day). We evaluated the liver function tests, serum lipids and BMI at the beginning of therapy, after 2 and 4 months. Liver biopsy was performed before and after therapy.

Results: In whole group, 37 patients had high level of serum aminotransferase and the lipid profile was: 13 cases with hypercholesterolemia, 7 cases with hypertriglyceridemia and 11 with both. In group A, mean value of serum ALT decreased from 89.19 + 22.7 U/l at baseline, to 52.12 + 16.8 U/l at 2 months. In B group, serum ALT was moderately reduced (in mean with 19.3 + 7.2 U/l) after 2 months and the cholesterolemia was significantly improved only in 5 cases (41.67%). In the A group the mean values of total-cholesterol, HDL and (TNF)-alpha were more decreased comparative with B group. After four months the normalization rates of ALT was 88.89% in A group and 73.33% in B group. Histopathologic examination indicated improvement the steatosis grade: 83.34% in A group and 70.84% in B group. Also, the fibrosis score was more reduced in the A group. The utilization of probiotics did not determined changes in BMI and LDL.

We could not establish a correlation between the values of serum aminotransferases and other parameters, but multivariate analysis showed that 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 combination of UDCA and probiotics 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.
**Rifaximin reduces the number, but not length, of hospital admissions in patients with refractory hepatic encephalopathy**

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**Introduction:** Overt hepatic encephalopathy (HE) is associated with significant morbidity and mortality and frequently requires hospital admission for treatment. Rifaximin, a non-absorbable antibiotic, has been shown in a RCT to reduce admissions in patients with recurrent HE. This study aimed to determine whether Rifaximin lead to a reduction in hospital admissions and length of stay in patients with HE, in an unselected secondary care cohort.

**Methods:** All patients with cirrhosis and recurrent HE prescribed Rifaximin in our institution were identified from outpatient prescriptions and electronic discharge summaries on the health board electronic record. Data on patient demographics, hospital admissions, MELD score and Child-Pugh status was collected and analyzed.

**Results:** 24 patients (16 male, 8 female) were identified; mean age 56 (30–74). Alcohol was the commonest etiology of cirrhosis (50%). Mean length of time on Rifaximin was 7 months (1–35). Mean MELD score was 13 (7–25) and Child-Pugh Status B. 10/24 patients were referred for transplant assessment; 1 underwent transplantation, 1 died pre transplant and 1 was rejected. 6/24 patients died at a mean of 5.5 months (1–11) post Rifaximin.

Prior to commencing Rifaximin, 48 admissions for overt HE occurred leading to a total of 485 days (mean 10.1) in hospital. Following Rifaximin therapy, 19 admissions totalling 313 days (mean 16.5) in hospital were observed. Therefore, mean hospital admissions reduced from 2 to 0.8 after commencing Rifaximin (p = 0.003). Excluding 6/24 patients that died; mean hospital admissions reduced from 1.9 to 0.8 (p = 0.017). Only 2/24 patients were non responders with no difference in number of admissions post Rifaximin.

**Discussion/Conclusion:** Rifaxamin for secondary prevention of overt HE leads to fewer HE related admissions but with longer hospital length of stays (LOS). Given recurrent HE is associated with poor transplant free survival this increased LOS possibly reflects deteriorating hepatic function and thereby performance status.
The role of prophylactic treatment with A. muciniphila in the acute alcoholic liver disease


Introduction: Alcoholic liver disease (ALD) is a major cause for liver-related deaths. ALD includes a clinical spectrum ranging from steatosis over alcoholic steatohepatitis (ASH) to liver fibrosis and hepatocellular carcinoma (HCC). Alcohol induces intestinal bacterial overgrowth and dysbiosis, these conditions are moreover associated with increased levels of lipopolysaccharides (LPS) and an altered gut barrier. Direct toxic impact of ethanol on the hepatocyte and translocation of LPS from the gut into the liver, play an important role in the pathogenesis of ALD. It was shown for A. muciniphila, a commensal bacterium, to restore gut barrier damage and thereby reducing systemic LPS levels.

Methods: Female wildtype mice were treated with $1.5 \times 10^9$ CFU of A. muciniphila on two days prior to alcohol administration (6 g ethanol/kg bodyweight). Eight hours after the gavage of ethanol, mice were sacrificed and samples were collected. To measure in vivo gut permeability, FITC-Dextran was gavaged four hours after alcohol administration, followed by concentration measurements in the serum.

Results: Ethanol administration led to significant higher levels of ALT ($p < 0.05$), whereas prophylactic treatment with A. muciniphila lead to significant decreased ALT levels ($p < 0.01$). We further investigated the numbers of A. muciniphila in stool samples. Alcohol administration reduced the number of A. muciniphila significantly ($p < 0.001$), independently if A. muciniphila was administered or not. Although we could see a reduction of FITC levels in probiotic treated mice, suggesting a restoration of the gut barrier, we couldn’t see improved endotoxemia. Furthermore we could see a trend towards a reduced expression of pro-inflammatory cytokines, although just TNF-alpha levels were significantly reduced by A. muciniphila treatment ($p < 0.05$).

Discussion/Conclusion: Our data indicate a potential role of A. muciniphila in the prophylactic treatment for ALD, but further experiments, in particularly for chronic alcohol consumption, should follow.
Evaluation of Ki-67 and PCNA expression in Crohn’s disease

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Introduction: Ki-67 and PCNA are proteins involved in cell cycle. The aim of this study was the comparison of expression of these two proteins as markers of cell proliferation in Crohn’s disease.

Methods: The study was conducted in a group of 12 patients with Crohn’s disease. Dysplastic changes were present in 5 cases. Immunohistochemical investigations were carried out using antibody against Ki-67 and PCNA. PCNA and Ki-67 expression were determined using the semiquantitative method. Expression for PCNA was absent (lack of reaction or reaction in < 40% cells), weak (reaction in 40–60% cells) average (reaction in 61–80% cells) or strong (reaction in 81–100% cells). Expression for Ki-67 was absent (lack of reaction or reaction in < 10% cells), weak (reaction in 10–40% cells), average (reaction in 41–70% cells) or strong (reaction in 71–100% cells).

Results: Cells without dysplasia in Crohn's disease showed a lack of protein expression of Ki-67 in 8/12 cases and poor in 4/12 cases while the PCNA protein showed only weak expression in 100% (10/10) of cases. The dysplastic cells expressing Ki-67 was on average 2/5 cases and strong in 3/5 cases, while the protein showed strong PCNA expression in 100% (5/5) cases.

Conclusion: Dysplastic cells show a greater expression of Ki-67 protein and PCNA than non-dysplastic cells. PCNA protein appears to be a better marker to distinguish dysplastic epithelium from non-dysplastic.

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The influence of anti-TNF-α agents on serum lipid profile and atherogenic index in patients with inflammatory bowel diseases

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Introduction: Cardiovascular morbidity appears to be increased in inflammatory bowel diseases (IBD). In patients with IBD, proinflammatory cytokine TNF-α can alter lipid profile causing dyslipidemia that promotes atherogenesis. The aim of this study was to identify long-term effect of anti-TNF-α therapy on lipid profile and atherogenic index in patients with IBD.

Methods: A total of 56 patients diagnosed as having IBD and treated with anti-TNF-α agents were evaluated by means of serum lipid profile. Atherogenic index was also calculated before biologic agent and then every six-month periods.

Results: The median follow-up period was 26.1 months. There was a significant increase in median total cholesterol at months 24 and 36 compared to baseline (165.5 mg/dL vs 176 mg/dL and 177 mg/dL, p = 0.01 and p < 0.001). There was also a significant increase in median triglyceride at months 24 and 36 compared to baseline level (97.5 mg/dL vs 133.5 mg/dL and 110.5 mg/dL, p < 0.001 and p = 0.02). A significant increase in median LDL-C levels between basal time and at months 12 and 36 was observed (95.0 mg/dL vs 99.0 and 103.5 mg/dL at months 12 and 36, p = 0.02). No significant change in HDL-C level was observed during follow-up period. Atherogenic index significantly increased at 36th month compared to baseline (3.89 vs. 4.09, p < 0.001).

Discussion/Conclusion: Significant changes were observed in cholesterol, triglyceride, LDL-C and atherogenic index of patients with inflammatory bowel diseases on anti-TNF-α after 36-month of treatment. Therefore, anti-TNFα treatment might affect lipid profile and atherogenic index which may contribute to cardiovascular morbidity.

References:
Long-term UDCA therapy in the patients with primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by a progressive course of cholestasis with inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. The underlying cause of the inflammation is believed to be autoimmunity. The prevalence of PSC is as high as 16.2 per 100,000 inhabitants. PSC is closely associated with inflammatory bowel disease, present in 60–80% of patients. Ursodeoxycholic acid (UDCA) is the most extensively studied therapy for PSC. In the present study we investigated the effect of UDCA on biochemical parameters and histological features in patients with PSC.

Methods: Twenty nine patients with clinical, biochemical, histological and radiological proven PSC were treated with UDCA 15 ± 2 mg/kg/day for a period of 48 months. Clinical, biochemical and histological parameters were followed for a period of 4 years.

Results: UDCA improved liver biochemistry study results and there were trends in histologic and cholangiographic improvement. UDCA improved clinical (jaundice, pruritus, fatigue) and biochemical markers of cholestasis and hepatocellular damage (aminotransferases, alkaline phosphatase, and serum bilirubin level) in 25 out of 29 patients with PSC. The beneficial effect of UDCA on the liver histology was assessed in 16/29 patients after minimum period of 12 months of therapy. Improvement in liver histology was found only in 5/29 pts.

Discussion/Conclusion: Our results suggest that long-term treatment with UDCA is beneficial in reducing disease activity in our PSC patients group, which may lead to prolongation of transplant free period. The use of UDCA appears to be safe and without side effects.
Prevalence of non-alcoholic fatty liver disease in inflammatory bowel disease patients treated with anti-TNF

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Introduction: TNFα may be involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) by promoting liver inflammation, insulin resistance and hepatocyte apoptosis. With our prospective study we aimed to investigate the role of anti-TNF administration on the prevalence of NAFLD in patients with inflammatory bowel disease (IBD).

Methods: We analyzed the prevalence of NAFLD found on ultrasounds performed in two groups of patients with IBD that are being followed in our Unit. Group A consisted of IBD patients receiving infliximab or adalimumab for the control of their disease and group B consisted of IBD patients that have never received anti-TNF therapy matched for age, sex, type of disease and extent of disease. From our analysis we excluded patients with a known history of liver disease and those reporting high alcohol consumption.

Results: A total of 67 patients were analyzed (Crohn’s disease: 35 patients, ulcerative colitis: 32 patients; mean age 44 ± 15 years). From these patients 34 were receiving anti-TNF therapy (group A) and 33 patients were not (group B). NAFLD was found in 12 patients of group A (35.3%) and in 16 patients of group B (48.5%). The difference between groups A and B as regards the prevalence NASH was not statistically significant (p = 0.27). A total of 67 patients were analyzed (Crohn’s disease: 35 patients, ulcerative colitis: 32 patients; mean age 44 ± 15 years). From these patients 34 were receiving anti-TNF therapy (group A) and 33 patients were not (group B). NAFLD was found in 12 patients of group A (35.3%) and in 16 patients of group B (48.5%). The difference between groups A and B as regards the prevalence NASH was not statistically significant (p = 0.27).

Discussion/Conclusion: A total of 67 patients were analyzed (Crohn’s disease: 35 patients, ulcerative colitis: 32 patients; mean age 44 ± 15 years). From these patients 34 were receiving anti-TNF therapy (group A) and 33 patients were not (group B). NAFLD was found in 12 patients of group A (35.3%) and in 16 patients of group B (48.5%). The difference between groups A and B as regards the prevalence NASH was not statistically significant (p = 0.27).
Evaluation of the presence of A-allele HERC2 (rs916977) and the presence of perianal fistula in Egyptian Crohn’s disease

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Introduction: Crohn’s disease (CD) is a multifactorial disease with a genetic background. (1) Perianal fistulae in CD rarely heal by themselves and lead to significant morbidity. (2) Till now, predicting the course of CD including the development of perianal complications has been a challenge. (3) An accurate prediction of the subgroups of patients most likely to have the worst outcomes will be very useful to individualize the management and select the ideal strategy for each patient. (4) Using genetic markers for risk stratification are more appealing compared to serologic markers or clinical parameters. And that is because they are present long before the disease onset and before any environmental factor plays a role. (5) Recent genome-wide association studies identified homozygosity for the A-allele at HERC2 (rs916977) was found to be associated with perianal penetrating disease behavior. (6) The prevalence of CD is rapidly rising in Egypt and there is no information about this polymorphism frequency in the Egyptian population. (7)

Methods: The AIM is to evaluate the presence of A-allele at HERC2 (rs916977) and its relation to the presence of perianal fistula in Egyptian patients having CD. We studied 50 CD patients in which, 10 cases were presented by Crohn’s complicated with perianal disease and 50 healthy controls. All included subjects were Egyptian in whom genotyping for the previously mentioned HERC2 SNP was performed. Clinical and demographic features were characterized.

Results: Analysis of the allele and genotype frequencies at (rs916977) on the HERC2 gene, showed no association with CD in Egyptian patients (P = 0.636); odds ratio: 0.588; CI 95% (0.191–1.814). There was no association between HERC2 genotype variant and disease phenotype based on the Montreal classification. Also, there was no association with gender, smoking history, surgical history perianal fistulae, and presence of extra-intestinal manifestations.

Discussion/Conclusion: These results suggest that the polymorphisms at (rs916977) on the HERC2 gene seem not to be involved in the genetic predisposition to CD in Egyptian population, and confirm that there are ethnic differences in the genetic background of CD. Replication studies by independent groups are necessary to elucidate the contribution of susceptibility genes to CD in different ethnic populations.
References:


Disclosure of Interest: None declared

Keywords: Crohn’s disease, genetic polymorphisms, perianal disease
Morphofunctional parameters of the gallbladder in patients with non-alcoholic fatty liver disease (NAFLD)

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Objective: To evaluate the functional state of the gallbladder (GB) in patients with NAFLD.
The study involved 26 patients with NAFLD. Inclusion criteria – evidence of hepatic steatosis by ultrasound exclusion

Research methods: All the patients underwent sonographic examination of the liver with the definition of the functional state of the gallbladder. The functional state of the GB was determined by dynamic sonography konvexen the transducer of 3.5 MHz by using the system of linear scan in a real time ultrasonic scanner expert class "TOSHIBA XARIO".

The results of the study: The majority of patients – 84.6 % showed an increase in the size of the right lobe of the liver to 145.41 ± 1.73 mm, the left lobe to 64.36 ± 2.30 mm. In patients with NAFLD the heterogeneity of the structure of the right lobe of liver and the nature hyperechonecity were mainly diffuse (88.64 %) and diffuse-focal in of 11.34 %. In the left lobe of the liver – 93.10% and 6.90%, respectively. Distal ultrasound attenuation was detected in 22 patients (84.61 %). The size of the gall-bladder were increased in 21 patients (80.76 %). The decrease in contractile function of the bladder was observed in 19 (73.07 %) patients. The length of the gallbladder 72.90 ± 3.68 mm, width 35.76 ± 3.56 mm. An increase of echogenicity of the wall of the bladder was detected in 26 (100 %) patients, there was a marked thickening of the wall up to 3.23 ± 0.13 mm. In 16 (61.5 %) patients surveyed the bladder cavity was inhomogeneous, due to the presence of echogenic sludge.
Nonalcoholic fatty liver disease detected by transient elastography in the patients with inflammatory bowel disease – A pilot study

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Background and Aim: Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease and is strongly related to all metabolic syndrome components. Its prevalence in patients with inflammatory bowel disease (IBD) is less known. Thus, our aim was to investigate the incidence of NAFLD in patients with IBD.

Methods: In this cross-sectional study we have analyzed 19 patients with IBD (10 UC and 9 CD). The controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) were used to detect and quantify liver steatosis and fibrosis with the help of transient elastography (TE) (FibroScan®, Echosense SA, Paris, France). NAFLD was defined by the presence of steatosis and CAP values $\geq 238$ dB/m, regardless of the presence or absence of any stage of fibrosis and exclusion of other secondary causes of chronic liver disease.

Results: The mean age of our patients was $46.5 \pm 16.4$ years. There were 10 men and 9 females. The mean values of CAP and LSM were $234.4 \pm 55.8$ dB/m and $5.7 \pm 2.5$ kPa, respectively. Of 19 analyzed patients 10 had NAFLD (CAP $\geq 238$ dB/m). There was a significant positive correlation between CAP measurements and waist circumference ($r = 0.927; p = 0.0003$) as well as between CAP measurements and patients body weight ($r = 0.702; p = 0.003$). On the other hand we did not found significant correlation among investigated liver tests (i.e. alanin-aminotransferase, aspartat-aminotransferase and gamma-glutamyl transferase) and CAP measurements.

Conclusion: According to our pilot study, it seems that IBD patients have a high prevalence of TE defined NAFLD. But further studies that will investigate the truly prevalence of NAFLD in IBD patients as well as studies that will give us answer what factors are related to NAFLD in IBD patients are urgently needed.
Most liver related deaths in India are caused by alcohol: An audit of liver mortality from tertiary care center in North India

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Introduction: Alcohol, hepatotropic viruses, and non-alcoholic steatohepatitis (NASH) are the most important causes of liver related deaths. The distribution of these causes among Indian patients dying of liver disease is unknown. This information will help in prioritizing healthcare efforts in preventing liver related deaths in India.

Methods: Records of all consecutive patients who had died due to liver-related causes in the Gastroenterology Department of Sir Ganga Ram Hospital, New Delhi, India, from Nov 2010 to Oct 2014 were analyzed. Patients dying due to non-hepatic cancers metastasizing to liver were excluded. Clinical presentation and immediate etiological causes of death were analyzed. In patients with multiple factors, the most immediate etiology was taken as the cause of death.

Results: Records of 401 consecutive patients were analyzed. Nine patients were excluded who had died of liver metastasis from non-hepatic cancers; hence 392 patients were included in the study (median age 50 [range 14–87] years, males 80%). Underlying chronic liver disease (CLD) was present in 86% (335/392) while in 14% (57/392) there was no underlying CLD. In CLD group most patients (71%, 237/335) had presented with complications of cirrhosis (such as end-stage liver disease, portal hypertension, sepsis etc.). Acute-on-chronic liver failure was the presentation in 29% (98/335) of CLD patients. Among patients without underlying CLD the most common presentation was with acute liver failure (68%, 39/57). Overall, the most common cause of liver-related death was alcohol, responsible for 30% (118/392) of deaths, followed by NASH/cryptogenic in 23% (91/392), hepatotropic viruses in 19% (73/392), bacterial/other infections in 12% (45/392), and drug-induced liver injury in 6% (24/392). In 5% cases the cause was some unidentified acute hepatic insult. The distribution of causes of death in various presentations is shown in table.

Conclusion: Alcohol is the most important cause of liver related deaths in India and NASH/cryptogenic cirrhosis is the second important cause. Since, both these causes are preventable by increasing public awareness and implementing life-style measures, urgent attention should be paid towards these measures.
Intestinal microvascular density (MVD) in active inflammatory bowel disease (IBD) in colonoscopic biopsies from adult patients – pathologic angiogenesis closely associated with progression of the disease

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Introduction: Studies conducted in the last decade have focused on the process of neoangiogenesis and vascular dysfunction as a fundamental component of inflammatory bowel disease (IBD) pathogenesis. Therefore, some publications are concerned with immunohistochemical (IHC) detection of angiogenesis in IBD patients.

Aim: The study objective was the qualitative assessment of intestinal microvascular density (determined by vessel count) detected by immunohistochemistry (IHC) using the angiogenic factor CD34 in consecutive colonoscopic bioplates from adult patients with histopathologically diagnosed active IBD as compared to non-inflamed mucosa of control subjects.

Methods: Twenty-one adult patients with active IBD (14 with ulcerative colitis [UC] and 7 with colonic Crohn’s disease [CD]) and 7 endoscopically normal patients were recruited to the current study. The colonoscopically obtained biopsies underwent routine histologic staining with Mayer’s hematoxylin and eosin (H&E) and immunohistochemical staining for the presence of endothelial cell marker CD34 (Clone QBEnd 10, Dako, Denmark). Intestinal MVD was assessed by microvessel count in the areas with diffuse and focal inflammation, IHC-visualized in 5 random fields of vision at 20 x zoom magnification. To statistical analysis used nonparametric Mann-Whitney U test.

Results: The quantitative assessment of vessels by IHC with the endothelial cell marker CD34 showed a considerable increase in the number of microvessels (angiogenesis) in the IBD-affected bowel as compared to endoscopically normal patients. In the areas with severe colonic inflammation in the two pathologies, UC and CD, there was a significant (P < 0.001) increase in vessel density (28.3 ± 7 vessels/field) compared to the areas of non-inflamed mucosa in control subjects (11.8 ± 1 vessels/field).

Discussion/Conclusion: Our quantitative IHC investigations indicate that the significant increase in intestinal vessel density is associated with progressive phases of IBD, which may be an important index of the disease severity.
Liver test abnormalities predict complicated disease behaviour in patients with newly diagnosed Crohn’s disease

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Backgrounds and Aims: In celiac disease, prevalence of liver test abnormalities (LTA) is higher in patients with more severe mucosal inflammation. In Crohn’s disease (CD), prognosis is related to the severity of mucosal inflammation. We investigated whether in newly diagnosed CD the presence of LTA predicts the occurrence of stricturing and/or perforating disease.

Methods: A retrospective cohort study was performed in patients who were newly diagnosed with CD between 2002 and 2011 in one tertiary referral hospital and two teaching hospitals. Complicated disease was defined as the occurrence of stricturing and/or perforating disease. Liver test abnormalities (LTA) were defined as a value of any one of alkaline phosphatase (AP), Gamma GT (GGT), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) over the upper limit of normal.

Results: 383 patients were included, of whom 34.1% had LTA. LTA were mostly mild (less than 2 x upper limit of normal). During 5-year follow-up, 33.1% of patients in the group with LTA developed complicated disease behaviour compared to 14.6% without LTA (p < 0.001). Presence of LTA was identified as risk factors for complicated disease behaviour (HR 2.4, 95% confidence interval (CI) 1.5–3.9, p < 0.0001) as well as for the need for hospitalization (HR 1.7, 95% CI 1.1–2.8, p = 0.023).

Conclusions: LTA at diagnosis of Crohn’s disease was an independent risk factor for development of complicated disease behaviour and need for hospitalization. Presence of liver test abnormalities may be a widely available, low cost instrument that helps identifying high-risk patients who could benefit from a top-down therapeutic regimen. This study demonstrates the importance of understanding gut-liver interactions.
Peculiarities of treatment the patients with nonalcoholic steatohepatitis combined with diabetes mellitus of the type 2 at the stage of sanatorium-resort rehabilitation

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The prevalence of nonalcoholic steatohepatitis (NASH) among patients with diabetes mellitus (DM) of the type 2 reaches 70–90%. However, the algorithms of sanatorium-resort patient’s treatment with this syntropy are not elaborated.

The aim is to optimize the treatment of NASH patients combined with DM type 2 at the stage of sanatorium rehabilitation.

The study involved 85 NASH patients combined with DM type 2 at the sanatorium “Birch Grove” (Myrhorod), of which 45 (53%) women and 40 (47%) men, age 55.2 ± 3.9 years. The average duration of NASH was 4.6 ± 2.4 years, DM – 7.2 ± 1.9 years. Patients examined at the beginning and at 21-24th day staying in the sanatorium, determining ALT, AST, alkaline phosphatase (ALP), triglycerides, bilirubin and cholesterol in serum.

Before treatment in patients observed increased activity of ALT in 2.8 times, ALP – 2.5 times, bilirubin – at 2.47 times, cholesterol at 1.98 times, triglycerides – to 2.03 times compared with healthy (p < 0.05). The level of glucose in the blood serum was 7.4 ± 1.3 mmol/l. Baseline treatment included diet therapy, intake Myrhorod mineral water (3–4 ml/1 kg patient), hydropathical procedures magnetoultrasonic therapy, correction of glycemia (biguanides, thiazolidinediones). Depending on the treatment complex patients distributed into two groups: I (n = 40) - basal therapy, II (n = 45) - baseline and treatment of essential phospholipids (EPL) i.v. bolus of 500 mg №10 with simultaneous oral EPL oral intake (1800 mg/day) 3 months.

At the 21–24th day treatment aminotransferase activity in patients group I remained higher than group II patients (ALT – 59.4 ± 4.03 IU/l, AST – 46.6 ± 3.3 IU/l against ALT – 38.2 ± 1.8 IU/l, AST – 34.9 ± 2.1 IU/l, p < 0.05). The level of ALP, bilirubin in patients group I exceeded the performance group II to 1.3 and 1.2 times respectively (p < 0.05). Against the background of therapy the serum of patients groups I and II decreased the concentration of cholesterol in 1.3 times, triglycerides – 1.5 and 1.7 times, fasting glucose level was 6.7 ± 0.45 and 6.1 ± 0.9 mmol/l (p < 0.05) respectively.

Thus the additional inclusion of EPL preparation into the medication complexes for patients with NASH in combination with DM type 2 at the stage of sanatorium-resort rehabilitation normalizes liver functional condition and effectively removes the manifestation of cytolytic and cholestatic syndromes, improves lipid and carbohydrate metabolism.
Rosuvastatin or ursodeoxycholic acid in the treatment of the non-alcoholic steatohepatitis in patients with acute myocardial infarction and metabolic syndrome?

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Non-alcoholic steatohepatitis (NASH) is often diagnosed in pts with acute myocardial infarction (AMI) associated with the metabolic syndrome (MS). Traditional dyslipidemia treatment of AMI pts is the statins assignment, which prolonged use may cause the increased serum transaminases activity. In order to decrease the cytolysis syndrome frequency on the statin therapy background more rational approach to the NASH treatment in AMI pts is to reduce the daily dose statin therapy with concomitant ursodeoxycholic acid (UDCA) use.

The aim was to study the rosuvastatin effectiveness in combination with UDCA in NASH pts with AMI associated with MS.

We examined 121 NASH pts with AMI (with and without Q), of which 38 women. The average age was 53.5 ± 3.4 years, body mass index – 36.4 ±3.9 kg/m²; waist circumference – 105.4 ± 10.5 sm. The NASH-test was used for the diagnosis of NASH. The dyslipidemia was confirmed by the cholesterol, triglycerides, high density (CLHD) and low density (CLLD) cholesterol lipoproteins concentration study. The HOMA index was 6.2 ± 2.4. According to the NASH-test results NASH and dyslipidemia were found in 47 (38.8%) patients.

38 pts (22 women and 16 men) with NASH were randomized into two groups according to the treat complex: group I (n = 18) – rosuvastatin 20 mg/day, group II (n = 20) – rosuvastatin 10 mg/day + UDCA 15 mg/kg/day on the AMI basic therapy background. The treatment course was 6 months.

After 4 weeks the increased ALT activity was found in 4(22.2%) pts of group I, the average in 1.9 times higher compared with baseline (p<0.05). The ALT activity normalization was noted in 18(90%) pts of group II, which before treatment was 2.1 times higher than normal.

After 6 months the ALT and GGTP activity was 1.3 and 1.5 times higher than normal in 5 (24.4%) pts of group I, while all the biochemical parameters normalization was noted in 100% cases in pts of group II. The blood cholesterol level reduction was noticed in group I from 7.9 ± 1.2 mmol/l to 6.8 ± 0.9 mmol/l, p < 0.05; withal CLLD decreased from 5.5 ± 1.4 mmol/l to 4.8 ± 1.6 mmol/l, p < 0.05.

Combined therapy with UDCA + rosuvastatin in pts of group II showed much more effective blood cholesterol concentration decrease from 8.1 ± 1.5 mmol/l to 6.4 ± 1.1 mmol/l, p < 0.05; withal CLLD decreased from 5.7 ± 1.5 mmol/l to 4.4 ± 1.3 mmol/l, p < 0.05.

The blood triglycerides concentration decreased in pts of group I in 1.3 times during therapy, group II – 1.5 times.

Early use of the lipid-lowering half the daily dose therapy combined with UDCA in NASH pts with AMI and MS provides the liver function tests normalization and concomitant atherogenic dyslipidemia effective decrease compared with the rosuvastatin assignment. These results are the convincing proof of the hepatocyte dysfunction leading role in the dyslipidemia pathogenesis.
Ursodeoxycholic acid in the treatment of alcoholic liver disease

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Introduction: Alcoholic hepatitis (AS) and alcoholic steatosis (AS) is associated with inflammation, liver cell necrosis, impaired liver function, and progression to alcoholic cirrhosis (AC). Ursodeoxycholic acid (UDCA) has been reported to be useful for patients with various liver diseases. In the present study we investigated the effects of long-term treatment UDCA in alcoholic liver disease (ALD).

Methods: 53 patients with clinical, biochemical and histological proven alcoholic liver disease were treated with UDCA 15 ± 2 mg/kg/day for a period of 36 months. The patients were selected in 3 groups: 21 with AS, 17 with AH and 15 with AC. Clinical symptoms (weakness, anorexia, weight loss, nausea, vomiting, right upper quadrant abdominal pain, jaundice, pruritus, fatigue), biochemical parameters (γ-glutamyl transpeptidase, aminotransferases, alkaline phosphatase, and serum bilirubin level) and histological parameters were followed for a period of 4 years.

Results: UDCA improved clinical symptoms in 51 out of 53 patients and biochemical markers of cholestasis and hepatocellular damage (GGTP, AST, ALT, alkaline phosphatase, and serum bilirubin level) in 46 out of 53 patients. The beneficial effect of UDCA on the liver histology was assessed in 29 out of 53 patients after minimum period of 12 months of therapy commonly in the patients group with AH and AS. Improvement was found only in 12/53 pts. with ALD, but not in the patients group with alcoholic liver cirrhosis.

Discussion/Conclusion: Our results strongly suggest that long-term treatment with UDCA improves biochemical and clinical parameters in alcoholic liver disease. Histological improvement was partial and in minority of the patients. The use of UDCA in the treatment of ALD appears to be safe and without side effects in our patients group.
Target-specific anti-pancreatic antibodies are frequent in patients with primary sclerosing cholangitis and associated with poor disease outcome

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Introduction: Glycoprotein 2 (GP2) and CUB zona pellucida-like domain 1 (CUZD1) belong to protein families involved in gut innate immunity processes and have recently been identified as specific targets of anti-pancreatic autoantibodies (PAsbs) in Crohn’s disease (CD). We aimed to determine the prevalence and prognostic potential of novel target-specific PAsbs regarding long-term disease course in a cohort of a primary sclerosing cholangitis (PSC) patients.

Methods: Sera of 69 PSC patients (median age [range]: 32 [5–79] years, concomitant IBD: 67% and cirrhosis: 20%) were tested by indirect immunofluorescence test (IIFT) system with GP2 and CUZD1 expressing transfected HEK 293 cells (anti-rPAG2 and rPAG1 IgA/IgG). Classical serologic markers of IBD were also assessed (pANCA and alFS IgA/IgG by IIFT, while ASCA IgG/IgA and anti-OMP Plus™ IgA by ELISA). A previously reported inflammatory bowel disease (IBD) patient cohort (CD: 264 and UC: 179) were the controls. Poor disease outcome was defined as orthotopic liver transplantation (OLTx) and/or liver-related death during the follow-up (median: 94 months).
Results: A total of 43.5% of PSC patients were positive for either of the two target-specific anti-PABs, with a significant difference compared to patients with CD (26.8%, $p < 0.01$) or UC (7.6%, $p < 0.001$). Distribution of the two types of PAbs was equal and one-third of the positive cases showed double positivity. Anti-GP2 antibody positivity was exclusively IgA type, while anti-CUZD1 antibodies were of both IgA and IgG isotypes. No difference was found in the frequency of PAbs according to the baseline disease characteristics. Positivity for the IgA subtype of anti-GP2, but not for the classical serologic markers, predicted a faster progression of the disease. In Kaplan-Meier analysis, anti-GP2 IgA positivity was associated with shorter time to OLTx and/or liver-related death (pLogRank < 0.01), and remained an independent predictor after adjusting for the presence of cirrhosis in Cox-regression analysis (HR: 4.31 [1.05–17.61]).

Discussion/Conclusion: Our small-scale study has shown that occurrence of target-specific PAbs is common in PSC. Association of IgA type anti-GP2 antibody with faster disease progression serves as an additional hint towards the significance of gut-liver interaction in the disease course of PSC.
The diversity of the alcoholic steatohepatitis associated diseases – A single-cause matter

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Introduction: Alcohol abuse generates numerous diseases and has a huge social and medical impact. The multi-varied effect of alcohol intake on the liver has remained, to the day, the most important pathology issue.

Methods: We have investigated and followed up 56 patients with alcoholic steatohepatitis admitted to our clinics from October 2014 to October 2015. The study aimed at identifying the diseases associated to the hepatic disease, as well as their influence on the treatment, the prognosis and the evolution of the disease.

Results: Out of the 56 patients, 30 had been re-admitted to hospital, while 26 were cases of newly diagnosed alcoholic steatohepatitis.
In the group of patients known to suffer from alcoholic steatohepatitis, 4 were infected with HCV (2 of them with hepatic cirrhosis alterations) and 2 were infected with HBV. Other associated diseases which had been reason for admission to hospital were acute pancreatitis (5 patients), acute respiratory infections (4 patients) and cardiac decompensation based on dilatative cardiomiopathy (2 patients). Other pre-diagnosed associated diseases, emerged as a consequence of alcohol abuse, were protein calorie malnutrition (7 patients), peripheral polyneuropathy (10 patients) and varied psychiatric disorders (12 patients).
In the group of patients who had been just diagnosed with alcoholic steatohepatitis, 1 patient also had HCV infection, 6 had withdrawal syndrome and 5 patients had nutritional deficiency anemia, peripheral polyneuropathies and protein calorie malnutrition.

Conclusions: The important associated diseases at the patients known to suffer from alcoholic steatohepatitis have been infections with hepatitis viruses (HCV and HBV), acute pancreatitis, respiratory infections and cardiac diseases. These require more frequent check-ups (viral concomitant infections and cardiac diseases), because they may result in the aggravation of the hepatic disease, in adaptive treatment and a more severe prognosis. Acute pancreatitis and respiratory infections are comorbidities with potentially serious evolution and require admission to hospital.
At the patients newly diagnosed with alcoholic steatohepatitis, the most frequent associations were psychiatric diseases and peripheral neurological manifestations owing to alcohol abuse.
Correlation of anemia prevalence in hospitalized patients with inflammatory bowel disease with disease activity and localization

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Introduction: Anemia is a significant extraintestinal manifestation of inflammatory bowel disease and is often associated with inflammation and disease exacerbation. We wanted to investigate the prevalence of anemia in patients hospitalized at our department and its correlation with disease activity and localization.

Methods: We retrospectively analyzed patients with inflammatory bowel disease hospitalized at the Department of Gastroenterohepatology, University Hospital Sarajevo, between November 2014 and December 2015 and evaluated the correlation between clinical scores of disease activity and localization with iron and hemoglobin deficiency.

We used the Spearman correlation coefficient to compare clinical disease activity defined by the Mayo score for ulcerative colitis and Harvey Bradshaw (HB) for Crohn’s disease with hemoglobin (Hgb) and iron (S-Fe) levels. χ-square test was used to analyze the interdependence between disease localization with Hgb and S-Fe levels.

Results: Out of 32 hospitalized patients, 73% had s-Fe below the lower threshold, and 87.5% had low Hgb levels. Neither Mayo nor HB score showed a statistically significant correlation with Fe deficiency (Mayo score – Fe: ρ = -0.139, p = 0.569 > 0.05, HB score – Fe: ρ = -0.111, p = 0.677 > 0.05) nor Hgb levels (Mayo score – Hgb: ρ = -0.133, p = 0.575 > 0.05, HB score – Hgb: ρ = -0.225, p = 0.482 > 0.05). The cross-tabulation between Fe and disease localization showed no statistically significant connection (Ulcerative colitis χ-square test 5.4 with p 0.51 > 0.05, Crohn’s disease χ-square test 1.1 with p 0.89 > 0.05).

Discussion/Conclusion: This pilot retrospective analysis showed no statistically significant connection between Fe and Hgb levels with clinical disease activity or disease localization, probably due to a small patient sample. However, it did show a negative correlation with the clinical score, although not statistically significant, and it showed a potential indirect correlation. Therefore, further studies are required for confirmation, using a bigger patient sample.
Association of PPAR-gamma2 Pro12Ala and ACE I/D genes’ polymorphisms with metabolic and immune disorders in obese patients with NAFLD and hypertension

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Introduction: Hepatic steatosis (HS) and arterial hypertension (AH) have multiple common mechanisms of development involving metabolic and immune changes. Among them, impairment or inhibition of receptor molecules controlling enzymes responsible for oxidation and fatty acids synthesis, appear to contribute to fat accumulation. However, HS is to some extend still accepted as a non-systemic pathology, rather than systemic disease, not limited to liver but involving interaction between genetically determined mechanisms of metabolism regulation and vascular inflammation. The aim of this study was to investigate the influence of Pro12Ala polymorphism of Peroxisome proliferator Activated Receptor Gamma (PPAR-γ2) gene and Insertion/Deletion (I/D) polymorphism of Angiotensin Converting Enzyme (ACE) gene on metabolic profile and cytokines in obese patients with common combination of HS and AH.

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

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

Discussion/Conclusion: Metabolic disorders in HS obese hypertensive patients are associated with PPAR-γ2 Pro-allele (carbohydrates) and ProPro-genotype (lipids). Presence of D-allele of ACE gene is associated with reliably higher TNF-α plasma levels.
A possible impact of Helicobacter pylori infection on non-alcoholic fatty liver disease

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Introduction: Relative data regarding Helicobacter pylori (Hp) infection in non-alcoholic fatty liver disease (NAFLD) are limited. The aim of this one-center, cross-sectional study was the evaluation of Hp infection in patients with NAFLD and its association with disease severity.

Methods: Twenty eight patients with biopsy-proven NAFLD (15 with simple non-alcoholic fatty liver [NAFL], 13 with nonalcoholic steatohepatitis [NASH]) and 25 matched healthy controls were enrolled. Blood samples for anti-Hp IgG and standard biochemical tests were obtained after overnight fasting, and 13C urea breath test was performed before liver biopsy in NAFLD group.

Results: Higher anti-Hp IgG serum levels (p = 0.038) were observed in NAFLD than in controls. Only two NAFLD patients were neither Hp IgG seropositive nor did they have a history of eradication treatment compared to 11 control subjects (p = 0.002). Both Hp infection (assessed by history of Hp eradication treatment and/or Hp IgG seropositivity) (p = 0.034) and log (HOMA-IR) (p = 0.007) could independently predict NAFLD in logistic regression analysis. There were similar rates of Hp IgG seropositivity or positivity in 13C urea breath test or their combination between NAFL and NASH patients. There were no significant differences in steatosis grade, fibrosis stage, lobular or portal inflammation, or ballooning, when NAFLD patients were divided according to Hp IgG seropositivity or 13C urea breath test positivity.

Discussion/Conclusion: Hp infection might represent one more hit contributing to the pathogenesis of NAFL, though not to the progression from NAFL to NASH. These results require further validation. If validated, eradicating Hp infection might have relative therapeutic perspectives in NAFLD treatment.
Comparison of MELD and Child-Pugh score short time prognostic significance in patients with decompensated liver cirrhosis: A Bosnian experience

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Introduction: Model for the end stage liver disease (MELD) score has gained broad acceptance over the traditional Child Pugh(CTP) score in predicting survival in patients with decompensated liver cirrhosis, although it’s short-term prognostic superiority has not been definitely confirmed. Predictive value of MELD has never been evaluated on patients with decompensated liver cirrhosis in Bosnia and Herzegovina. The aim of this study was to examine the MELD score, the CTP score and creatinin modified CTP score in Bosnian patients with decompensated liver cirrhosis and to determine their correlation and significance in prediction of 6 months survival.

Methods: A total of 80 patients with decompensated cirrhosis referred to our department for further treatment and evaluation were included in the study. The end point was 6 months mortality. Accuracy in assessing 6 months mortality was obtained by measuring area under the receiver operating characteristics (ROC) curves.

Results: Average age at the time of referral was 57.93. The majority of patients were male 62%. Hepatitis B was cause of liver disease at 35% of patients. The 6 months mortality was 36%. Area under the ROC curve for the prediction of 6 month mortality of CTP, creatinin modified CTP and MELD score were, respectively 0.761, 0.846 and 0.872. Correlation was strongest between CTP and creatinine modified CTP score (0.951) and lowest between MELD and CTP score (0.617).

Discussion/Conclusion: MELD score was found to be better predictor of 6 month mortality than CTP and creatinin modified CTP score in patients with decompensated liver cirrhosis.
Proliferating cell nuclear antigen PCNA is associated with dysplasia in ulcerative colitis

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Introduction: The probability of developing cancer in ulcerative colitis in 5-fold greater than in the general population. Detected numerous groups of dysplasia may prevent the development of cancer by execution a total colectomy.

Methods: The study included a group of 19 patients with ulcerative colitis, who was classified histologically as: positive for dysplasia (10 patients) and negative for dysplasia (9 patients). The expression of PCNA protein was assessed by means for immunohistochemical method using monoclonal anti-PCNA antibody (clone PC10, DAKO). PCNA expression was determined using the semiquantitative method and assessed as weak (lack of reaction or reaction present in < 40% cells) and strong (reaction visible in > 40% cells).

Results: Protein expression in cells that do not show dysplasia in ulcerative colitis was strong in 1/19 (5.3%) patients and weak in 18/19 (94.7%) patients. By contrast, in dysplastic cells in ulcerative colitis PCNA protein expression was strong in 8/10 (80%) patients, and weak in 2/10 patients (20%). Overall assessment of PCNA expression in both the non-dysplastic and dysplastic cells in ulcerative colitis shows that a strong expression of PCNA protein correlate the presence of dysplasia (p = 0.001).

Conclusion: PCNA expression is associated in formation of dysplastic changes in ulcerative colitis. Increased proliferation of dysplastic cells may predispose to the occurrence of mutation and increase the risk of cancer.
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.
Can the inflammatory bowel disease biologics registry lead to improved quality of care?

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Introduction: A Registry is a systematic collection of data about a disease or diseases. For some years there has been a desire amongst the gastroenterology community to develop a comprehensive Registry of patients with inflammatory bowel disease (IBD). However, there has been no coordinated national approach. In this study we will review the grounds behind setting an IBD registry; suggest a methodological approach, and the ways to maintain its continuity.

Methods: We searched the PubMed, Embase and PsycINFO databases for articles describing the development and/or evaluation of one or more of the registries in IBD. We assessed these registries using a standardized checklist.

Results: There have been several registries of biological therapy in Crohn’s disease like TREAT registry for Infliximab®, Registry study for Adalimumab®, the Rotherham IBD management software, and the Inflammatory Bowel Disease Information System (IBDIS). The British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHN) has established a registry of paediatric IBD in late 1990s but it was only maintained for a few years. Recently the UK IBD registry was established following the second round of the UK IBD audit, and the launch in Feb 2009 of the National IBD Service Standards.

Discussion/Conclusion: In summary, having a successful IBD registry will ensure efficient patients monitoring and follow up. It will also support data collection for audit and research purposes. However, any registry should be tailored for individual users’ needs to ensure their engagement and participation. A few difficulties associated with setting a wide IBD registry may include lack of clinicians’ participation or interest, costs related to setting and maintaining the registry, providing enough time to use the registry and data quality assurance.
Clinical implications of alpha-1-antitrypsin deficiency causing iron overload and cirrhosis

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Introduction: Liver cirrhosis is frequently associated with iron overload and reduced plasma concentrations of alpha-1-antitrypsin. These changes can either be explained by impaired hepatocellular function, or indicate genetic alpha-1-antitrypsin deficiency (A1ATD) and hemochromatosis (HC) as underlying causes of liver disease. Our recent finding that alpha-1-antitrypsin reduces hepatic expression of the iron hormone hepcidin via inhibition of matriptase-2 in hepatocytes provides a mechanism for the association of A1ATD with HC. To study the clinical implications of this association, a cohort of patients with A1ATD and HC was characterized. The molecular mechanism of A1AT controlled hepcidin expression was investigated in a cell model for A1ATD that was created by genome editing.

Methods: HFE genotype and alpha-1-antitrypsin concentrations were assessed in a cohort of 863 patients with elevated serum iron parameters (ferritin > 300 & transferrin saturation > 50%). The CRISPR/Cas9 (pLentiCrisprV2) system by lentiviral transduction and puromycin selection was used to create an A1ATD cell line. A site close to the start codon was targeted and dysfunction of the disrupted A1AT gene was confirmed by western blotting.

Results: Among 863 patients with hyperferritinemia and elevated transferrin saturation 19 patients (2%) had an alpha-1-antitrypsin concentration of < 0.8 g/l. None of the patients was homozygous for the hemochromatosis associated HFE mutation p.Cys282Tyr. The prevalence of liver cirrhosis in this group was 95% (18/19). Of 18 patients with liver cirrhosis, 16 (89 %) had at least one Z-allele and 3 patients were ZZ homozygotes and 2 SZ compound heterozygotes, which supports the notion that A1ATD is the cause rather than a consequence of advanced liver disease in this cohort. To study the mechanism how A1ATD causes iron overload, a cell model for A1ATD was employed. Targeted disruption of the SERPINA1 gene encoding A1AT in HepG2 cells is associated with a significantly reduced hepcidin mRNA expression, when compared to HepG2 control cells.

Discussion/Conclusion: Genetic A1ATD can be considered a modifier of disease expression in patients with non-HFE hemochromatosis. Studies in a cell model suggest that iron overload is caused by reduced hepcidin expression caused by A1ATD.
Treatment of spontaneous bacterial peritonitis in a local hospital

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

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

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

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

Discussion/Conclusion: The mortality rate in our hospital was (57%). In our study, the median MELD score was > 40. Developing Hepatorenal syndrome and high Creatinine at SBP presentation were the main mortality predictor with mortality of 90%.
A case of Mirizzi’s syndrome

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Introduction: A 68 years old lady with known endometrial cancer referred from oncology to the on call medical team with jaundice. She was feeling unwell, lethargic and has loss of appetite for few days. She also noticed dark discoloration of her urine. This patient had endometrial cancer which was treated with total abdominal hysterectomy and bilateral salpingio-oopherectomy few months ago and was awaiting adjuvant chemotherapy. Other past medical history include left mastectomy for breast cancer twenty years ago, hypothyroidism and epilepsy. On examination, she was jaundiced but there were no other signs of chronic liver disease. Abdomen was soft with mild tenderness in the right upper quadrant area. No organomegally was present. Chest and cardiovascular examination were unremarkable.

Blood test showed white cell count of 14.8, Hb 132, platelet 312, Bilirubin 137, ALT 364, Alkaline phosphatase 429, Albumin 38, protein 71, and CRP 242.

She was treated for biliary sepsis with antibiotics. Ultrasound scan of abdomen showed a mass which could be a lymph node or metastases causing dilatation of the biliary tree. CT scan of abdomen showed inflammation at fundus of gall bladder, calculus at the neck of gall bladder/cystic duct, intra and extra duct dilatation secondary to CBD obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) was performed.

Methods: ERCP showed normal cholangiogram with suggestion of external compression at junction of CBD and CHD. A 9 cm stent was passed into the CHD with good bile drainage. Patient undergone laparoscopic cholecystectomy following the ERCP.

Results: From the CT scan result and the ERCP finding the case was diagnosed as Mirrizi’s syndrome that resulted from external compression of CBD by gall stones leading to mechanical obstruction

Discussion/Conclusion: This case report highlights that Mirizzi’s syndrome can be misdiagnosed as metastatic cancer or enlarged lymph node.
A case of amoebic liver abscess

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Introduction: A 24 year old student from Bangladesh presented with history of sweating, loss of appetite for a month, fever, shortness of breath and, epigastric pain. He does not have any past medical history. He came to the UK 2 years ago. On examination, he looked pale and wasted, observations were normal, BCG scar was noted on his right upper arm, and had tenderness in the right upper quadrant. He was spiking temperature mainly at nights. Basic blood tests and blood cultures were done

Methods: CT scan showed 6.8 cm rounded mass between the left and right lobe of the liver. The possible diagnoses were an amoebic liver abscess or a hydatid cyst. Stool examinations was normal. Serological tests showed positive Amoebic IFAT and a negative Hydatid ELISA test. These findings strengthened the diagnosis of Amoebic liver abscess

Results: From the CT scan and serology test the diagnosis of amoebic liver abscess was established. Patient was started on oral metronidazole and oral cefalexin for a total of 10 days. A letter was sent to his GP to start him on Diloxanide fumerate for 10 days. The patient responded well to treatment.

Discussion/Conclusion: This is a case of 24 year old Bangladeshi student who presented with Amoebic liver abscess. It is the most frequent extraintestinal manifestation of *Entamoeba histolytica* infection and is an important cause of space-occupying lesions of the liver, mainly in developing countries. It is rare in the U.K. and it is mostly seen in immigrants or travelers. Complications include Pleuropulmonary infection, Cardiac involvement, bacterial superinfection, and rupture into peritoneal organs and mediastinum. Uncomplicated amebic liver abscesses can be treated with amebicidal drug therapy alone, metronidazole, tinidazole, emetine, and dehydroemetine are active in invaded tissues.
Maintenance of antithrombotic therapy post endoscopy for acute upper gastrointestinal bleeding is associated with improved clinical outcomes

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Introduction: Antithrombotic drugs (antiplatelets and anticoagulants) are often stopped following acute upper gastrointestinal bleeding (AUGIB). In the UK, guidelines have recently advocated resuming aspirin after AUGIB,[1] but their position on non-aspirin antithrombotics is less clear. We aimed to assess if maintenance of antithrombotic therapy following AUGIB correlated with improved clinical outcomes.

Methods: We identified patients on antithrombotic therapy who underwent gastroscopy for suspected AUGIB at University Hospital Birmingham whilst on antithrombotic therapy between May 2013 and November 2014 and performed follow-up until March 2015. Clinical outcomes were measured after endoscopy and discharge, and included cause-specific mortality, thrombotic events, rebleeding, and any adverse event. Patients were stratified according to whether antithrombotics were maintained or discontinued. Data comparisons were performed using Fisher’s Exact and t-test, with Kaplan-Meier analysis to estimate follow-up outcome.

Results: 132 patients were included for analysis, of which 118 survived until discharge. Antithrombotic use consisted of aspirin monotherapy (43%), oral anticoagulants (27%), dual antiplatelet therapy (DAPT) [16%], thienopyridine monotherapy (10%), and other (4%). Antithrombotic maintenance, defined as resumption within 72 hours of endoscopy or prior to discharge, was observed in 51%. Older age, aspirin monotherapy and peptic ulcer disease were significant predictors of antithrombotic discontinuation.

Mean follow-up after discharge was 286 days. The overall mortality rate was 22%, with in-hospital mortality of 11%, with a rebleeding rate over follow-up period of 8.2%. Overt bleed-related mortality (n = 3) was overshadowed by cardiovascular mortality (n = 16) [p = 0.005]. Discontinuation of antithrombotic therapy post endoscopy was associated with increased thrombotic events (RR 5.5, p < 0.001), reduced rebleeding (RR 0.5, p = 0.35), and increased incidence of any adverse event (RR 2.1, p = 0.005).

Discussion/Conclusion: In a single centre observational study, mortality from thrombotic causes following AUGIB is high. Maintenance of antithrombotic therapy, including non-aspirin regimens, is associated with improved thrombotic outcomes and reduced mortality.

1. NICE CG 141, Acute upper gastrointestinal bleeding: management, June 2012.
Bacterial infections in alcoholic liver cirrhosis

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Introduction: Several studies have demonstrated that alcoholic cirrhosis was associated with major defects of immune system. It must be assumed that the rate of infection is higher in alcoholic liver cirrhosis. Aim of this study was to determine the frequency of bacterial infections in alcoholic cirrhosis.

Methods: We performed two studies: prospective (included 151 cirrhotic patients who admitted to the Department of Gastroenterology between 2009 and 2011) and retrospective (308 hospitalized cirrhotic patients, who died of cirrhosis complications from 2000 to 2010). From each study were selected patients with alcoholic cirrhosis (83 and 192 respectively). Cirrhosis was clinically and/or histologically confirmed. The types of infections were defined according to the standard criteria.

Results: Out of the 151 patients (general group of prospective study), 67 patients (44.4%; 95% CI: 36.3–52.7%) had various infections. The most frequent infections were following: urinary tract infections (UTI) – 20.5; 95% CI: 14.1-26.9, pneumonia – 15.9; 95% CI: 10.1–21.7 and spontaneous bacterial peritonitis (SBP) – 10.5; 95% CI: 2.6–18.5. Bacterial infections were found in 129 patients (41.9; 95% CI: 36.3–47.6) by results of retrospective study (n = 308). The most frequent were pneumonia – 31.5; 95% CI: 26.3–37.0, UTI – 8.8; 95% CI: 5.9 –12.5 and sepsis – 4.2;  95% CI: 2.3–7.1. The structure and frequent of bacterial complications among patients with alcoholic cirrhosis are presented in table.

Table: Types of bacterial infections in patients with alcoholic liver cirrhosis in both study

<table>
<thead>
<tr>
<th>Infections</th>
<th>Patients with alcoholic cirrhosis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>prospective study n = 83</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>All cases</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
</tr>
<tr>
<td>UTI</td>
<td>15</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>8</td>
</tr>
</tbody>
</table>

* abscess various localization, cholangitis, osteomyelitis and endocarditis

Discussion/Conclusion: The frequency of bacterial infections in patients with alcoholic cirrhosis was comparable to the general group cirrhotic patients. In structure of prospective study UTI and pneumonia prevailed, for retrospective study it was pneumonia.
Especially the accumulation of fat in patients with non-alcoholic fatty liver disease

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Introduction: Nonalcoholic fatty liver disease (NAFLD) is associated with metabolic factors, including obesity.

Methods: The amount of body fat in different areas from 40 patients with NAFLD (24 men, 16 women aged 41–73 years) was investigated using the method of Dual-energy x-ray absorptiometry (DEXA) (GE Medical Systems LUNAR) program „Body composition“. Median body mass index was 34 kg/m², waist circumference for men – 113 cm, for women – 102 cm.

Results: The survey showed an increase in the percentage of total body fat both men (Me 34.54%) and women (Me 45.3%). The prevalence of android obesity among the men and 13/24 women was discovered (table).

Table: The results of the patient fat survey using the program «Body composition»

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Me</th>
<th>P25</th>
<th>P75</th>
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<tbody>
<tr>
<td>Men: total fat, %</td>
<td>34.54</td>
<td>29.71</td>
<td>38.65</td>
</tr>
<tr>
<td>Women: total fat, %</td>
<td>45.31</td>
<td>42.05</td>
<td>47.35</td>
</tr>
<tr>
<td>Men: trunk fat/total fat</td>
<td>0.56</td>
<td>0.58</td>
<td>0.65</td>
</tr>
<tr>
<td>Women: trunk fat/total fat</td>
<td>0.55</td>
<td>0.51</td>
<td>0.60</td>
</tr>
<tr>
<td>Men: android region (% fat)</td>
<td>43.4</td>
<td>39.41</td>
<td>47.75</td>
</tr>
<tr>
<td>Women: android region (% fat)</td>
<td>50.35</td>
<td>46.85</td>
<td>54.51</td>
</tr>
<tr>
<td>Men: android fat/gynoid fat</td>
<td>1.27</td>
<td>1.27</td>
<td>1.51</td>
</tr>
<tr>
<td>Women: android fat/gynoid fat</td>
<td>1.03</td>
<td>0.97</td>
<td>1.08</td>
</tr>
</tbody>
</table>

However, the correlation analysis did not find a relation between amount of fat, including android, and activity in the liver: ALT and total fat \(r_s = -0.28\), android fat \(r_s = -0.14\), android fat/gynoid fat \(r_s = 0.50\), AST and total fat \(r_s = -0.33\), android fat \(r_s = -0.13\), android fat/gynoid fat \(r_s = 0.60\).

Discussion/Conclusion: Body fat excess is not the only factor of NAFLD progression.
Intestinal dysbiosis as a leading factor in dyslipidemia progression in patients with nonalcoholic steatohepatitis

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The relevance of nonalcoholic steatohepatitis (NASH) is caused by the absence of characteristic clinical symptoms and, therefore, late disease diagnosis with high risk of metabolic disorders. The presence of overgrowth bacterial syndrome (OBS) can contribute to the violation of the liver functional state and potentiating dyslipidemic changes in patients with NASH.

**Aim:** To examine the OBS incidence and role in cytolytic syndrome severity and nature of lipid profile changes in patients with NASH.

**Materials and Methods:** The study involved 78 patients with NASH aged 36–68 years, including 41 (52.6%) men and 37 (47.4%) women. In order to diagnose OBS the hydrogen breath test was performed, according to its results patients were divided into 2 groups: I (n = 46) – patients with NASH, combined with OBS; II (n = 32) – patients with NASH. The functional liver state indicators were evaluated in serum: alanine (ALT), aspartic (AST) aminotransferase, γ-glutamyl transpeptidase (GGTP), alkaline phosphatase (ALP), total bilirubin (TB), blood lipid profile: total cholesterol, triglycerides (TG), HDL-C, LDL-C.

**Results:** OBS diagnosing rate in patients with NASH is 58.9%. And in the group of patients with NASH and OBS combination the ALT activity was increased in 3 times, AST – in 2.1 times, GGTP – in 2.7 times compared with the norm (68.1 ± 19.41 U/l, 48.1 ± 21.22 U/l and 83.1 ± 20.9 U/l respectively; p ≤ 0.05). In the group II the ALT activity was increased in 2.4 times, AST – in 1.8 times, GGTP – in 2.2 times compared with the norm (52.1 ± 20.14 U/l, 43.2 ± 20.57 U/l and 67.3 ± 18.2 U/l respectively; p ≤ 0.05). The ALP and total bilirubin were within normal limits in both groups. In group I the increased level of cholesterol was found in 35 (85.3%) pts and TG level – in 31 (75.6%) pts, amounted 6.9 ± 1.32 mmol/l and 2.71 ± 1.4 mmol/l respectively. In the group II the increased concentration of cholesterol was noted in 18 (56.25%) pts, TG – 14 (43.75%) pts: 5.79 ± 1.07 mmol/l and 2.19 ± 1.08 mmol/l respectively. Indicators of HDL-C, LDL-C did not differ in the groups.

Thus, NASH in 58.9% of cases is accompanied with OBS, that leads to the increased activity of cytolytic syndrome and is accompanied with a higher frequency of dyslipidemic violations development.
The role of nonalcoholic fatty liver disease in the progression of atherogenic dyslipidemia in patients with ischemic heart disease

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Non-alcoholic fatty liver disease (NAFLD) can be considered a part of the metabolic syndrome (MS), which is a risk factor for the ischemic heart disease (IHD) development and progression. The metabolic risk factors determination and their elimination is one of the priority areas of secondary acute cardiovascular events prevention. Thus, the further research of the dyslipidemic changes in the blood of patients with IHD based on the coexistent NAFLD presence or absence are required to identify risk factors for the progression of atherogenic dyslipidemia and conduct timely prevention of the IHD complications.

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

The study involved 64 pts with IHD (stenocardia II functional class), aged 30–79 years, including 18 (28%) women, 46 (72%) men. The duration of IHD was 2–10 years. The coexistent NASH was found in 22 (34.4%) pts, the duration of NAFLD – 3–7 years. The viral and alcoholic nature of liver injury was excluded. Pts didn’t take statins. Depending on the NAFLD presence pts were divided into 2 groups: I (n = 22) – IHD pts with the concomitant NAFLD; II (n = 42) – IHD pts without NAFLD. 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-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), total bilirubin.

The liver functional state changes in pts of group I were characterized by the increased ALT to 68.2 ± 24.4 U/l, AST to 42.1 ± 18.7 U/l, GGT to 78.4 ± 23.6 U/l; ALP activity and total bilirubin concentration were within normal limits (169.4 ± 47.1 U/l, 16.1 ± 4.09 mmol/l respectively). In pts of group II all liver functional state parameters did not differ from the norm. In the group I the increased total cholesterol level was observed in 19 (86.3%) pts, increased TG level – in 15 (68.2%) pts: 6.3 ± 1.42 mmol/l and 2.7 ± 1.25 mmol/l, respectively, the AI was 5.1 ± 1.42. In the group II the increased concentrations of total cholesterol in 22 (52.4%) pts, TG – in 16 (38.1%) pts: 5.02 mmol/l and 1.88 ± 1.04 mmol/l, respectively; the AI was 4.19. The HDL-C and LDL-C levels in the both groups did not differ.

In pts with IHD and the concomitant NAFLD compared with the group without NAFLD more pronounced dyslipidemic violations were revealed, that are considered to be risk factors for the IHD development and progression.
Mucosal angiogenesis in active inflammatory bowel disease (IBD): Immunohistochemical study of CD31 and CD34 expression in colonoscopic biopsies. The first report in pediatric patients

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Introduction: The role of endothelium in the initiation and propagation of IBD pathology has been recently emphasized. It is believed that endothelial expansion in newly formed vessels in IBD, mediated by inflammatory growth factors, cytokines and chemokines, is an indication of active gut disease and is closely related to disease severity.

Aim: The present study was to assess immunohistochemically (IHC) mucosal angiogenesis (mucosal microvascularization), i.e. analyze the expression of the endothelial cell biomarkers, CD31 and CD34, in the areas with actively inflamed intestinal mucosa in colonoscopic biopsies from children with histopathologically diagnosed active IBD as compared to endoscopically normal mucosa.

Methods: Nineteen children with active IBD were included in the study (12 with ulcerative colitis [UC] and 7 with colonic Crohn’s disease [CD]) and 7 controls. The colonoscopically obtained biopsies underwent routine staining with Mayer’s hematoxylin and eosin (H&E), and IHC staining for the angiogenic factors, CD31 (Clone JC70A, Dako, Denmark) and CD34 (Clone QBEnd 10, Dako, Denmark).

Results: The IHC study for CD31 and CD34 showed markedly increased number of microvessels and individual positive cells located in the areas with diffuse and focal inflammation in biopsies with histopathologically diagnosed active colonic IBD mucosa as compared to normal colonic mucosa. We found that the intestinal endothelium in newly formed and inflamed vessels, both in UC and in colonic CD, was particularly well seen in IHC staining. Although routine H&E staining was also helpful in the assessment of mucosal angiogenesis, it was insufficient to identify budding vessels. It should be emphasized that in active IBD mucosa, proliferating and expansive intestinal endothelial cells in newly formed and inflamed microvessels demonstrated by far stronger immunosuppression than in control subjects, especially towards the endothelial cell marker CD34.
Discussion/Conclusion: The current IHC study indicates that pathological angiogenesis constitutes an integral morphological component of active IBD and is closely related to disease severity in pediatric patients. Since so far no similar reports concerning pediatric patients have been available, further research is required to define the mechanisms that underlie the vascular dysfunction and its role in the initiation and propagation of IBD pathology.
Polymorphisms of IL-4 (C-590T), TNF-α (G-308A), PRSS1 (R122H) and CFTR (delF508C) genes, NAFLD, ASH, pancreatitis and cholestasis

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Introduction: Both non-Alcoholic fatty liver disease (NAFLD) and alcoholic steato-hepatitis (ASH) cause significant influence on various digestive system organs, while cholestasis and pancreatitis are not associated with these pathologies though they have many common pathogenetic mechanisms. Combination of NAFLD or ASH with acute pancreatitis and cholestasis is frequently out-of-interest for most investigators. Furthermore, causative role of genetic factors for such morbid combination is generally unclear, while intensive testing of different genetic polymorphisms is underway. We hypothesize that NAFLD, ASH, cholestasis syndrome, and pancreatitis may have common genetic predispositions. The aim of the study was to check the possible relationship of cholestasis syndrome in patients with acute pancreatitis combined with NAFLD or ASH, depending on the gene’s polymorphism of IL-4 (C-590T), TNF-α (G-308A), PRSS1 (R122H) and CFTR (delF508C), etiology and gender.

Methods: Study involves 101 patients: 19 (18.8%) women, and 82 (81.2%) men. 64 (63.37%) patients with ASH and 37 (36.63%) with NAFLD. Genetic polymorphisms studied by PCR.

Results: GG-genotype of PRSS1 gene was in 100% of study group individuals; CFTR gene’s NM-genotype – in three patients (2.97%), NN-genotype – in 98 (97.03%); only NN-genotype observed in control. TNF-α gene’s GG-genotype identified in 81.19%, GA-genotype in 18.81%. IL-4 gene’s CC-genotype found in 58 patients (57.43%), CT genotype in 34 (33.66%) patients, TT-genotype in 9 (8.91%) patients; in control – 26 (65%), 11 (27.5%) and 3 (7.5%), respectively ($\chi^2 < 1.0, P > 0.05$). Activity of cholestatic syndrome was significantly higher in TT-genotype carriers of IL-4 gene (rs2243250) compared to C-allele carriers (TC, CC) and was characterized by higher gamma-glutamyl transferase – 1.9 and 1.58 times (NAFLD subgroup) and 2.06 and 1.53 times (among women); total bilirubin – 1.85 and 2.13 times (ASH subgroup) and 1.66 and 1.87 times (among men); direct bilirubin – 2.81 and 3.22 times (ASH subgroup) and 2.47 and 2.96 times (among men), respectively.

Discussion/Conclusion: This study has established no associations between PRSS1 (R122H), CFTR (delF508) and TNF-α (G-308A) genetic polymorphisms and cholestatic syndrome, pancreatitis etiology and gender. However, IL-4 gene’s TT-genotype carriers have significantly higher expression of cholestasis, especially in ASH patients, depicting the common pathogenetic role of pro-inflammatory cytokines.
Intestinal dysbiosis, hemodynamic peculiarities of mesenteric vessels, non-alcoholic fatty liver disease and genetic polymorphisms of ACE (I/D) and AGTR1 (A1166c) genes

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in developed countries (6–35%) with about 30% prevalence in the United States between 2011–2012 as shown in the recent study using the National Health and Nutrition Examination Survey. Obesity, diabetes (DM), hypertension (AH), and other systemic diseases frequently combine with NAFLD due to multiple similar pathogenesis mechanisms. The aim of this study is to find possible connections between intestinal dysbiosis, hemodynamic peculiarities of mesenteric vessels, NAFLD and ACE (I/D) and AGTR1 (A1166c) genes' polymorphisms.

Methods: Study involves 104 patients: 50 (48.1%) women, and 54 (51.9%) men. Mean age – 53.2 ± 8.7. NAFLD, AH, and DM diagnosis and management according to AASLD/ACG/AGA, ASC/ESH and ASD Guidelines, respectively. Microbiology included taxonomic group identification and population levels determination with 33.3% variation as dysbiosis single step deviation. Visceral blood vessels status evaluated sonographically. Genetic polymorphisms studied by PCR.

Results: Ischemic changes in blood vessels were characterized by decrease of time overage velocity (reliable in D-allele carriers of ACE gene and C-allele of AGTR1 gene in 1.4–1.94 times, p < 0.05), increase of peak systolic and end diastolic velocity (not depending on genotypes of analyzed genes in 1.5–3.05 times, p < 0.05) and peripheral resistance by Gosling index (2–2.35 times, p < 0.05). Dysbiosis severity strongly correlated with NAFLD, AH severity in D (ACE) and A (AGTR1) allele's carriers while changes in blood vessels correlated with dysbiosis severity with weaker dependence on genotypes. AGTR1 gene's CC-genotype carriers had the highest risk of abdominal vessels changes. Severity of dysbiosis moderately and strongly r = 0.61–0.83, p ≤ 0.04–0.001) positively correlated with NAFLD, AH and DM severity.

Discussion/Conclusion: While genetic predisposition to NAFLD is considered to be proved, the role of genetic factor explaining systemic changes in NAFLD patients is controversial. Both ACE and AGTR1 genes' polymorphisms has no direct influence on liver but determine changes of blood vessels and microbiota. It causes respective influence on metabolic profile with correlation of dysbiosis and disease severity.
Gut barrier failure biomarkers are associated with poor disease outcome in patients with primary sclerosing cholangitis

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Background: Gut-liver interaction is a pathogenetic feature of primary sclerosing cholangitis (PSC), however the effect of this cross-talk on the disease course has not been fully elucidated. A panel of serological markers that reflect either mechanical or immunological gut barrier dysfunction were assessed in a cohort of patients with PSC. Association of these markers with disease specific characteristics and the long-term disease course was evaluated.

Patients and Methods: Sera of 69 PSC patients (median age [range]: 32 [5–79] years, concomitant IBD: 67% and cirrhosis: 20%) were assayed for intestinal fatty acid-binding protein (I-FABP) and various immunoglobulin A (IgA) molecules (IgA1, IgA2 and secretory[s] IgA, anti-F-actin [AAA IgA] and anti-gliadin [AGA IgA/IgG]) by ELISA. Poor disease outcome was defined as orthotopic liver transplantation (OLTx) and/or liver-related death during the follow-up (median: 94 months). 155 healthy subjects (HCONT) and 179 ulcerative colitis (UC) patients were the controls.

Results: In PSC, median I-FABP level was similar to that in HCONT (216 vs. 244 pg/mL) but higher than in UC (176 pg/mL, p < 0.05). slgA level (95.7 μg/ml) was two- and three-fold higher compared to either the HCONT or the UC (p < 0.001, for both). 28.4%, 9% and 20.9% of PSC patients were positive for AAA IgA, AGA IgA and AGA IgG, respectively. Frequencies of AAA IgA (p < 0.001, for both) and AGA IgG (p = 0.01,
for both) but not AGA IgA were significantly higher compared to HCONT and UC. Regarding disease-specific characteristics, slgA level was significantly lower in PSC patients with concomitant IBD (80.7 vs. 160.4 μg/ml). In Kaplan-Meier analysis only target-specific IgAs and slgA (> 175 μg/ml) were associated with a shorter time to OLTx and/or liver-related death, whereas total IgA or IgA2/IgA1 ratio and I-FABP were not. All markers remained significant after adjusting for the presence of cirrhosis in Cox-regression analysis (HR [95% CI]: 3.67 [1.05–12.82] for slgA, 5.15 [1.27–20.86] for AAA IgA and 5.07 [1.25–20.54] for AGA IgA). Combining these markers further enhanced their predicative potential (HR [95% CI]: 11.30 [2.84–44.93] for ≥ 2 marker positivity).

**Conclusion:** In our small-scale study, gut-related IgA type antibodies identified PSC patients with progressive disease, further highlighting the importance of the gut-liver interaction in PSC.
Simultaneous presence of IL-17A-producing T cells and FoxP3+ T cells in IBD mucosa

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Introduction: The dynamic interplay between Th17-producing T cells and FoxP3+ T regulatory cells is essential for maintaining gut homeostasis. Cytokines related to these T cells subsets are essential mediators of tissue damage closely connected to the intestinal inflammation in inflammatory bowel disease (IBD) patients. However, a clear picture of the underlying interactions in the mucosa is still missing especially in human IBD.

Methods: We examined the mRNA relative quantities (RQ) and protein levels of IL-17, IL-23, TGFβ1, IL-6, IL-10 as well as the transcriptional marker FoxP3, in paired colonic mucosa samples derived from 23 patients with ulcerative colitis (UC), 14 with Crohn’s disease (CD) and from 12 healthy persons.

Results: We observed that IL-6, TGFβ1 and FoxP3 genes were overexpressed (RQ > 15) in inflamed mucosa from IBD patients in contrast to their expression in normal mucosa from non-IBD patients. Our data showed that both UC and CD share similar expression profile with significant differences between higher gene expression of IL-6 in inflamed tissue in UC patients (p = 0.025) compared to the adjacent normal mucosa in the same patients (RQ = 6.3), and increased IL-23 gene expression in CD patients in inflamed versus adjacent normal mucosa (RQ = 28.09, p = 0.046). Moreover, we observed significant increase of TGFβ1 expression in CD patients alone (RQ = 22.09, p = 0.041). Coefficients of correlations between paired target genes in inflamed and in adjacent normal tissue from IBD patients varied from moderate to strong (r = 0.859) (p < 0.05). The serum levels of IL-23 (p = 0.008), TGFβ1 and IL-6 were higher in IBD patients compared to non-IBD patients with similar levels of IL-17A and IL-10 in both groups.

Discussion/Conclusion: Our results showed differences in the expression of some mRNA-encoded cytokines which drive naïve T cells either to Th17 or Tregs. The specific expression profile obtained in mucosa of IBD patients including TGFβ1 and IL-6, essential for Th17 development, with upregulated IL-17, IL-23 mRNA and protein levels, simultaneously with IL-10 and the transcription factor FoxP3, which are characteristics of Tregs, suggests indirectly for the presence of both Tregs and Th17 cells in the mucosa, and this profile may represent a transcriptional hallmark for IBD.
Serum ferritin level is associated with diseases severity and markers of bacterial translocation but not with long-term disease course in cirrhosis

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Introduction: Elevated serum ferritin (SF) level is a commonly recognized phenomenon in non-hemochromatosis cirrhosis because of hepatic iron accumulation and systemic inflammation. Bacterial translocation (BT) is a characteristic feature of cirrhosis and significant cause of chronic inflammatory state. Effect of BT on SF has not been elucidated so far. In a prospective referral cirrhotic cohort, we aimed to evaluate the association of SF to serologic and genetic markers of BT and prognostic potential of SF in the long-term disease course.

Methods: Sera of 254 consecutive stable outpatients with cirrhosis (male: 50%, alcoholics: 63.4%, median age: 55 years and MELD score: 11) were assayed for the concentrations of ferritin by sandwich-type immunoassay and a panel of BT markers (C-reactive protein [CRP], lipopolysaccharide-binding protein [LBP]) and IgA type antimicrobial [ASCA, anti-OMP Plus™] or autoantibodies [ANCA]. Common NOD2 variants were determined by TaqMan polymerase chain reaction. A 5-year follow-up observational study was conducted to assess a possible association between SF and development of decompensation events (ascites formation, variceal bleeding, hepatic encephalopathy or systemic bacterial infection) and mortality.

Results: SF level was associated to male gender (median [No vs. Yes]: 87 vs. 148 µg/l, p = 0.003), disease severity, as rated by the Child-Pugh stage (median [ChildA/B/C]: 78, 148 and 340 µg/l, p = 0.001) or the presence of ascites (median [ascitesNo vs. Yes]: 90 vs. 171 µg/l, p = 0.016). SF level showed significant correlation with CRP (p = 0.008) and LBP (p < 0.027) level but was not significantly different between patients with or without specific IgA antibodies or NOD2/CARD15 mutation. High SF level (> 400 µg/l), however, did not predict the development of the disease specific complications and nor the long-term mortality in univariate Cox analysis.

Discussion/Conclusion: In the present study, we demonstrated that SF level is a marker of advanced disease stage in cirrhosis and somewhat correlates with serologic markers of BT. However, determination of SF level did not provide additional help in risk stratification of stable outpatients with cirrhosis.
Lipocalin 2 drives neutrophilic inflammation in alcoholic liver disease

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Introduction: Alcoholic liver disease (ALD) is the main reason for end-stage liver disease and the stage of alcoholic steatohepatitis (ASH) is a life-threatening condition which is characterized by systemic neutrophilia and hepatic neutrophil infiltration. Lipocalin-2 (LCN2), also termed neutrophil gelatinase-associated lipocalin (NGAL), was initially discovered in granules of neutrophil granulocytes and lately was shown to play a role in liver homeostasis and experimental hepatic injury. Aim of this study was to investigate LCN2 function in experimental ALD.

Methods: Human and mouse serum and liver samples were investigated for LCN2 expression. To dissect the pathogenic role of LCN2, 6- to 8-week-old female C57BL/6 wild-type (WT) and Lcn2-deficient (Lcn2⁻/⁻) mice underwent experimental ALD (via feeding the Lieber-DeCarli diet containing 5% [vol/vol] ethanol or a control diet for 2 weeks ad libitum). Adoptive transfers of WT and Lcn2⁻/⁻ neutrophils were used to distinguish between hepatic and neutrophil-derived LCN2 in ALD.

Results: LCN2 was upregulated in serum and liver samples in human and mouse ALD. We identified leukocytes and especially neutrophils as the cellular source of LCN2. Lcn2⁻/⁻ mice were protected from ALD which was associated with diminished neutrophil infiltration. Adoptive transfer of WT and Lcn2⁻/⁻ neutrophils demonstrated that neutrophil-derived LCN2 is required for neutrophilic inflammation in ALD.

Discussion/Conclusion: LCN2 is upregulated in human and mouse ALD and is required for neutrophilic inflammation in alcoholic liver injury. Therefore, targeting LCN2 may be a novel treatment option in ALD.
Reversal of murine alcoholic steatohepatitis by pepducin-based functional blockade of interleukin-8 receptors

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Introduction: Alcoholic steatohepatitis (ASH) is a life-threatening condition with short-term mortality up to 40%. It features hepatic neutrophil infiltration and blood neutrophilia, and may evolve from ethanol-induced breakdown of the enteric barrier and consequent bacteremia. Signaling through CXCR1/2 G-protein-coupled-receptors (GPCR), the IL-8 receptors, is critical for the recruitment and activation of neutrophils. We have developed short lipopeptides (pepducins) which inhibit post-ligand GPCR activation precisely targeting individual GPCRs.

Methods: Experimental alcoholic liver disease was induced by administering alcohol and a Lieber DeCarli high-fat diet. CXCR1/2 GPCRs were blocked via pepducins either from onset of the experiment, or after disease was fully established. Hepatic inflammatory infiltration, hepatocyte lipid accumulation, and overall survival were assessed as primary outcome parameters. Neutrophil activation was assessed by MPO activity and liver cell damage by AST and ALT plasma levels. Chemotaxis assays were performed to identify chemoattractant signals derived from alcohol-exposed hepatocytes.

Results: Here we show that experimental alcoholic liver disease is driven by CXCR1/2-dependent activation of neutrophils. CXCR1/2-specific pepducins not only protected mice from liver inflammation, weight loss and mortality associated with experimental alcoholic liver disease, but therapeutic administration cured disease and prevented further mortality in fully established disease. Hepatic neutrophil infiltration and triglyceride accumulation was abrogated by CXCR1/2 blockade. Moreover CXCL-1 plasma levels were decreased with the pepducin therapy as was the transcription of hepatic IL-1beta mRNA.

Discussion/Conclusion: We propose that high circulating IL-8 in human AH may cause pathogenic overzealous neutrophil activation, and therapeutic blockade via pepducins merits clinical study.
Restoration of low adipose PNPLA3 concentrations after bariatric surgery

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Introduction: Obesity and associated diseases such as non-alcoholic fatty liver disease (NAFLD) are increasing dramatically worldwide. Recently, the I148M polymorphism in the Patatin-like phospholipase domain-containing protein 3 (PNPLA3; also known as adiponutrin [ADPN]) gene has been associated with alcoholic liver disease (ALD) and NAFLD. The PNPLA3 variant was shown to affect hepatic fat content and liver inflammation whereas the biological function of PNPLA3 is not clearly understood. The aim of our study was to examine whether weight loss (induced by laparoscopic gastric banding [LAGB]) affects hepatic or adipose PNPLA3 expression in severely obese patients.

Methods: Hepatic and subcutaneous adipose tissue samples from twenty severely obese patients were investigated for PNPLA3 expressions before and 6 months after LAGB. In vitro experiments were performed to study the effect of lipopolysaccharide (LPS) and tumor necrosis factor alpha (TNFα) on PNPLA3 expression in primary CD14+ monocytes, SGBS adipocytes, and Hep3b hepatoma cells.

Results: PNPLA3 expression was about 9-fold higher in the liver compared to subcutaneous adipose tissue. Subcutaneous adipose tissue PNPLA3 expression was about 7-fold increased 6 months after LAGB whereas hepatic PNPLA3 expression remained unaffected. Accordingly, pro-inflammatory signals such as LPS and TNFα strongly reduced the PNPLA3 expression in monocytes and TNFα also reduced its expression in adipocytes. PNPLA3 expression in Hep3b hepatocytes was unaffected by pro-inflammatory signals.

Discussion/Conclusion: Here we show that that adipose tissue PNPLA3 expression is restored by LAGB-induced weight loss and PNPLA3 expression in monocytes and adipocytes can be abolished by inflammatory signals. Further studies are necessary to investigate the role of PNPLA3 in the adipose tissue.
Analysis of CCR9 and β7 in patients with primary sclerosing cholangitis and ulcerative colitis

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Introduction: Primary sclerosing cholangitis (PSC) has a strong association with inflammatory bowel disease, and in particular, ulcerative colitis (UC). It has been suggested that bowel specific CCR9+ β7+ T-cells are involved in the pathophysiology of PSC, implicating the gut-liver axis, and indeed α4β7 inhibitors are effective in UC. We sought to evaluate the proportions of these lymphocyte populations in the peripheral blood and bowel of PSC/UC, UC, and controls.

Methods: Patients with PSC, UC only, liver controls (“LC” – NASH, PBC, AIH, and ALD), celiac disease and healthy controls (HC) were identified through the Oxford PSC Database and the Oxford Gastrointestinal Illnesses Biobank (REC: 11/YH/0020). Peripheral blood was taken to isolate peripheral blood mononuclear cells (PBMC). Colonic lamina propria infiltrating lymphocytes (LPILs) were isolated from fresh intestinal biopsies taken at colonoscopy from a subset of patients. PBMC and LPILs were stained with a lymphocyte marker panel of antibodies, including CCR9 and β7, and multicolor flow cytometry was performed. The proportion of CD4+ and CD8+ lymphocytes which were CCR9 or β7 positive was compared among groups.

Results: PBMC were analysed for 53 patients (PSC = 20, UC = 4, LC = 16; Celiac = 8; HC = 5). There was no significant difference in CCR9 expression on CD4+ peripheral blood T-cells between patients with PSC and controls nor on CD8+ T-cells. In PSC patients vs. HCs, there was a trend towards higher amounts of β7 positive CD4+ T-cells (18.46% vs. 11.02%) and CD8+ T-cells (28.12% vs.13.13%), but this was not statistically significant.

On analysis of LPILs from a subset of the patients, there was a higher proportion of CCR9+ CD4+ T-cells in UC inflamed colon (47.30%) compared with PSC inflamed colon (21.97%) and HC uninfamed colon (29.14%). This was true also for CD8+ T-cells (CCR9+ CD8+ T-cells: UC = 65.10%, PSC/UC = 21.3%; HC = 24.11%). There were no significant differences noted among groups with regards to beta7 positivity in LPILs.

Discussion/Conclusion: CCR9+ T-cells are enriched in the colon as compared with the peripheral blood, and it appears they may be particularly enriched in the inflamed colon of UC patients compared with healthy controls and those with PSC/UC. These differences were not borne out as strongly with β7 positive T-cells, although more samples are required. This indicates a potential role for therapies targeting the CCR9/β7 pathway, and potentially a fundamental difference in the lymphocyte phenotype in PSC/UC versus UC, which may involve rehoming of CCR9+ T-cells to the liver. Further samples are currently being analyzed to further these findings.
Radiology in IBD, for medical trainees

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Introduction: CT and MRI findings in IBD patients are often critical in determining their ongoing management. As well as informing about disease progression, images may dictate need for treatment escalation, as well as need for surgery. Despite years of MDTs and X-ray meetings, it can be hard to grasp the interpretation of classic radiological findings in IBD patients. This is because radiology does not form a part of Core Medical Training, hence registrars may be ill-prepared for being asked their opinion on images. Additionally CT and MRI images are usually accompanied by a helpful radiologist report, thereby allowing doctors to progress with minimal knowledge of this area.

Methods: I obtained anonymized X-ray, CT and MRI images from ulcerative colitis and Crohn’s patients that I have cared for at Charing Cross Hospital. I went through the images and sought advice from a radiologist about what each image showed. Many images had already been discussed in our X-ray meetings. In doing this I collated some excellent images depicting some classic findings.

Results: The poster aims to educate doctors with an interest in IBD about the radiological appearance of different presentations of IBD.

Discussion/Conclusion: I feel that with core knowledge and pattern recognition skills, most doctors could confidently be informed by looking at the images from a CT/MRI scan. I think this level of understanding is crucial for getting the most out of X-ray meetings and informing discussions with colleagues, as well as informing early management. This can be important as not all scans are reported the same day, also patients may attend clinics with unreported scans. Understanding radiology also increases understanding of anatomy, which can be directly related to the clinical picture. This poster aims to help address a gap in training by providing a bank of interesting images for trainees.
The Doppler flow study for the assessment of the alcoholic liver lesion

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Introduction Clinical examinations, laboratory tests are not fully useable for diagnosis the period of alcoholic liver disease. There are following steps of liver damage caused by alcohol:
steatosis → steatohepatitis → parenchymal fibrosis → symptomatic cirrhosis.
Invasive methods: biopsy, laparoscopy are necessary for final diagnosis. Doppler flow measurements of liver vessels create new interesting non-invasive diagnostic possibilities.

The aim of the study: The Doppler flow examination of the liver vessels in alcoholic patients and to compare results to non-alcoholic patients.

Patients and Methods: 30 alcoholic patients (pts) suffering different abdominal complains were examinated by Doppler method. The long lasting – sometimes few years alcohol abuse (above 100 g daily) – was confirmed in anamnesis. Other diseases (HCV infection, diabetes mellitus, obesity, treated hiperlipide mia, others) which could influence the liver vessels assessment were excluded. Following parameters of liver vessels were analyzed: portal flow, arterial flow, relation portal/arterial flow and relation portal/2D USG presentation, hepatic vein flow, presence of pathological flow. 50 non-alcoholic pts were control group.

Results: We have observed numerous Doppler flow pathologies. The most useful for the grade liver injury were: reversed or lack portal flow, the presence of collaterals, decreased portal flow and increased arterial flow, others.

Comments: There is real clinical problem to establish the advancement of alcoholic liver lesion. The prognostic importance has detection of periportal fibrosis. The liver biopsy is not popular and sometimes is contraindicated due to coagulopathy. The advanced fibrosis causes hepatic vessels flow disturbances: portal flow decrease or reverse, pathological portal/arterial relations, the presence of collaterals. The quantitative measurement of hepatic vessels flow are: portal flow velocity, hepatic artery systolic and diastolic flow measurement, hepatic circulation index (artery flow/portal flow), pulsatility or resistive indexes of hepatic artery, congestive index (portal vein surface/mean portal flow) and vascular index (portal flow/hepatic arterial pulsatility index). The considerable decrease of portal flow usually below 10 cm/s, hepatic circulation index above 3.5 may be used as indicators of periportal fibrosis.
Conclusions:
1. Numerous Doppler flow disturbances give possibilities to assess qualitative and quantitative grade of alcoholic liver damage.
2. The Doppler flow should be analyzed as part of the duplex and triplex USG examination of the liver.
3. The range of Doppler flow abnormalities is often independent from clinical and biochemical liver tests.
Recurrent primary sclerosing cholangitis after liver transplantation: Case report

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease that progresses to end-stage liver disease and is closely associated with ulcerative colitis (UC). Orthotopic liver transplantation (OLT) has become the only effective treatment option for these patients, but still the PSC recurrence is found with an incidence of 8.6 to 47%.

Methods: This is a prospective observational review of a 51 years old male who had been diagnosed with UC and PSC with liver cirrhosis in 2003. OLT was performed in 2011.

Results: In October 2003 the patient was admitted in Emergency department with complains of jaundice and diarrhea. PSC was diagnosed based on radiological, histological and biochemical findings – alkaline phosphatase 1138 U/L, GGT 636 U/L, ALAT 272 U/L, bilirubin 46 mmol/L. UC was approved by clinical course, colonoscopy and histological findings. Before 2011 several endoscopic retrograde cholangiopancreatographies and percutaneous transhepatic cholangiographies were done with metal and plastic stents placements. Due to the progression of diseases patients had liver cirrhosis (Child-Pugh Score 11, MELD 13), hypoalbuminemia, ascites and portal hypertension with esophageal varices. In January 2011 OLT (modified of Piggyback technique) with a Roux-en-Y biliary reconstruction was performed. After two weeks alkaline phosphatase was 231 U/L, GGT 183 U/L, ALAT 31 U/L, bilirubine 25 mmol/L. Patient regularly receives tacrolimus and mycophenolate mofetil based as post OLT immunosuppresion, as well as mesalazine of 1600 mg and ursodeoxycholic acid 500 mg per day. In December 2015 the patient developed recurrent sclerosing cholangitis, as assessed by MR imaging of biliary tree and biochemical findings – alkaline phosphatase 412 U/L, GGT 722 U/L, ALAT 58 U/L.

Discussion/Conclusion: Patient and transplant survival following OLT is close to 80% at 5 years. Still patient and transplant survival do not appear to be negatively affected by disease recurrence. The pathogenesis of recurrence PSC remains unexplainable.
Multifactorial risk prediction model for refractory Crohn’s disease patients

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Introduction: Crohn’s disease is a multifactorial inflammatory disease with a progressive relapsing remitting course. Refractoriness to conventional therapy is a common and worrying problem in CD patients. Therefore, we aimed to investigate whether risk model combining common CD susceptibility loci, age of diagnosis and smoking status can sufficiently predict a subgroup of CD patients who are poor responders.

Methods: In our retrospective study, we included 132 CD patients from Slovenian population with complete information about genotyping data, clinical status (70 refractory, 62 non-refractory), smoking status and age of diagnosis. Association study was performed for 74 single nucleotide polymorphisms (SNPs). We constructed genetic risk scores (GRS) as a sum of risk alleles multiplied by their weights (logOR). Genetic and non-genetic information was included in logistic regression model and discriminatory accuracy was measured by an area under ROC curve (AUC). Nagelkerke R Square was used to determine total CD variability explained by a model.

Results: The highest discriminatory accuracy in genetic prediction was achieved with 30 SNPs, AUC of 0.71. Patients in the highest GRS quartile were likely to develop CD more than 3 years earlier than those in the lowest quartile, however age difference was not significant (26.88 vs 30.24, p = 0.315). Risk model combining non-genetic factors (smoking, age of diagnosis) achieved AUC of 0.64, whereas only smoking was statistically significant independent factor (OR 3.47, 95% CI 1.55 to 7.77, p = 0.003). Combined risk model (GRS, smoking, age of diagnosis) yielded AUC of 0.75 and explained 21.5% of total disease variance in refractory CD patients.

Discussion/Conclusion: Our results suggest that common risk variants in combination with external factors may be useful discriminators between refractory and non-refractory CD patients. In the future, inclusion of other gene-environment factors may improve risk prediction and explain higher proportion of total CD variance.
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