Therapeutic Strategies in Diseases of the Digestive Tract – 2015 and Beyond

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THERAPEUTIC STRATEGIES IN DISEASES
OF THE DIGESTIVE TRACT –
2015 AND BEYOND

Freiburg, Germany
October 16 – 17, 2015

Scientific Organization:
M.J. Bruno, Rotterdam (The Netherlands)
E.M. El-Omar, Aberdeen (Scotland)
P. Ginès, Barcelona (Spain)
D.K. Podolsky, Dallas (USA)
J. Schölmerich, Frankfurt (Germany)
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Session I

Esophagus
Eosinophilic esophagitis (EoE) has been defined as a “chronic, immune/antigen-mediated, esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation”. A peak value of ≥ 15 eosinophils/high power field has been defined as histologic diagnostic cutoff. Other conditions associated with esophageal eosinophilia, such as gastro-esophageal reflux disease (GERD), PPI-responsive esophageal eosinophilia, or Crohn’s disease need to be ruled out before EoE can be diagnosed. Males are affected more frequently than females and most of the patients have concomitant allergies. Currently, the EoE prevalence is about 1/2000 inhabitants in Westernized countries. The first EoE patients have been described only 2 decades ago. Despite this short period, considerable progress has been made regarding the understanding of the pathophysiology, natural history, assessment of disease activity, and with respect to evaluating different therapeutic options. EoE is now recognized as chronic inflammatory disorder which can lead to esophageal remodeling processes with reduced compliance and stricture formation which represents the main risk factor for food bolus impactions. The therapeutic options can be summarized with the 3 “D's” which stand for “drugs, diets, and dilation”. Of note, as of yet there is no EoE-specific drug that has been approved by regulatory authorities. This is, among other reasons, related to the lack of validated outcome measurement instruments until recently. Swallowed topical steroids such as budesonide or fluticasone represent the standard of care for treating symptomatic pediatric and adult EoE patients with inflammatory activity. Trials evaluating different biologic therapies, such as anti-IL13, or anti-IgE, are currently on the way. As a non-pharmacologic alternative, different dietary regimens exist. Dilation can offer long-lasting symptomatic response in case of stricturing EoE but does not have any impact on the underlying inflammation. This review highlights the latest insights regarding pathophysiology and diagnosis of EoE.

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Endoscopic management of early cancer

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The last decades, endoscopic treatment of both early squamous as well as Barrett’s neoplastic lesions in the esophagus has evolved as a valid and less invasive alternative to surgical resection. Endoscopic resection (ER) is the cornerstone of endoscopic therapy. Next to the curative potential of ER by removing neoplastic lesions, ER also serves as a diagnostic tool. The relatively large tissue specimens obtained with ER enable accurate histological staging of a lesion, allowing for optimal decision making for further patient management. Endoscopic resection can be performed using a number of different techniques, from cap-based techniques to endoscopic submucosal dissection.

After focal ER for early neoplasia in Barrett’s esophagus, additional treatment of the remaining Barrett’s epithelium is advised to prevent metachronous lesions during follow-up. Complete eradication of Barrett’s mucosa can be achieved by additional endoscopic resections or thermal ablation. Endoscopic resection for visible lesions, complemented with radiofrequency ablation to remove the entire Barrett’s segment has proven its efficacy and safety in a number of international, multicenter studies. Also long-term outcomes of this combined approach support the use of endoscopic therapy as the primary treatment strategy for early Barrett’s neoplasia.

Although its efficacy and safety have been proven for early Barrett’s neoplasia, there is debate whether or not endoscopic therapy also has a place in the management of Barrett’s cancer infiltrating the superficial submucosa. Currently, surgical treatment is still considered the gold standard in these cases, given the substantial risk of lymph-node metastasis. However, results of recent studies suggest that patients with ‘low-risk’ sm1 cancer (well differentiated, without lymphovascular invasion) may be treated endoscopically. Given that most patients with ‘low-risk’ sm1 cancers are elderly and often suffer from significant comorbidities, endoscopic treatment may be considered a safe and effective alternative to surgery in these cases.
Achalasia: From bench to POEMs

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Achalasia is a primary esophageal motility disorder with an estimated annual incidence of 1 per 100,000 persons. It is characterized by absence of esophageal peristalsis and failure of the lower esophageal sphincter (LES) to relax upon swallowing, resulting in progressively severe dysphagia for solids and liquids, regurgitation, aspiration, chest pain and weight loss. Achalasia results from a loss of enteric neurons, most likely due to an autoimmune reaction in patients with a particular immunogenetic background. To date, three manometric subtypes have been identified based on high resolution manometry. To what extent these subtypes also indicate differences in underlying pathophysiological mechanisms is however unclear. As achalasia cannot be cured, treatment is confined to disruption of the LES to improve bolus passage and thereby relieving symptoms. The two most commonly used treatment modalities available for this purpose include pneumatic dilation and laparoscopic Heller myotomy. Both treatments have been shown repeatedly to be successful, however, success rates decline in time, most likely due to progression of the disease. A recent European randomized trial provides objective data indicating that both treatments are equally effective. In view of these data and the low incidence of the disease, the choice between these two treatments should be based on the expertise and experience available. Since recently, excellent short-term success rates have been reported with a new endoscopic technique, i.e. peroral endoscopic myotomy (POEM). However, longer follow-up data are absolutely needed before accepting this technique as new treatment option for achalasia in clinical practice.
From reflux to cancer

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Reflux esophagitis causes Barrett’s metaplasia, an abnormal esophageal mucosa predisposed to adenocarcinoma. Medical therapy for reflux esophagitis focuses on decreasing gastric acid production with proton pump inhibitors. We have reported that reflux esophagitis in a rat model develops from a cytokine-mediated inflammatory injury, not from a caustic chemical (acid) injury. In this model, refluxed acid and bile stimulates the release of inflammatory cytokines from esophageal squamous cells, recruiting lymphocytes first to the submucosa and later to the luminal surface. Emerging studies on acute reflux esophagitis in humans support this new concept, suggesting that reflux-induced cytokine release may be a future target for medical therapies. Sometimes, reflux esophagitis heals with Barrett’s metaplasia, a process facilitated by reflux-related nitric oxide (NO) production and Sonic Hedgehog secreted by squamous cells. We have shown that NO reduces expression of genes that promote a squamous cell phenotype, while Hedgehog signaling induces genes that mediate the development of the columnar cell phenotypes of Barrett’s metaplasia. Agents targeting esophageal NO production or Hedgehog signaling conceivably could prevent the development of Barrett’s esophagus. Persistent reflux promotes cancer in Barrett’s metaplasia. We have reported that acid and bile salts induce DNA damage in Barrett’s cells. Bile salts also cause NF-κB activation in Barrett’s cells, enabling them to resist apoptosis in the setting of DNA damage, and likely contributing to carcinogenesis. Oral treatment with ursodeoxycholic acid prevents the esophageal DNA damage and NF-κB activation induced by toxic bile acids. Altering bile acid composition might be another approach to cancer prevention.
Session II

Stomach
Functional dyspepsia and gastroparesis

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Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. The most frequently encountered causes of these symptoms are mechanical obstruction (pyloric stenosis), iatrogenic disease, gastroparesis, functional dyspepsia, cyclical vomiting and rumination syndrome.

Principles of management include:
First, exclude mechanical obstruction with imaging, typically, with upper gastrointestinal endoscopy and, increasingly, with CT or MR enterography.
Second, consider iatrogenic causes of gastroparesis:
a. Intake of opiates, even newer generation opioid medications (e.g. tramadol) or ones with µ-opioid agonist and norepinephrine uptake inhibition (e.g. tapentadol), retard gastrointestinal or colonic transit.
b. Use of cannabis is associated with cannabinoid hyperemesis during withdrawal.
c. In type 2 diabetes mellitus, several medications that improve postprandial hyperglycemia also retard gastric emptying: amylin analog and GLP-1 agonists, not dipeptidyl peptidase IV (DPP IV) inhibitors (-gliptins).
d. Post-surgical: Vagotomy or vagal injury may result from fundoplication or bariatric surgery.
Third, perform an accurate gastric emptying test: scintigraphy or stable isotope GEBT.

The most common causes of gastroparesis are neuropathic disorders such as diabetes, idiopathic, post-vagotomy, and scleroderma among myopathic disorders. Prokinetics and anti-emetics are the mainstays of treatment.

Functional dyspepsia is characterized by the same symptoms as gastroparesis; in addition to delayed gastric emptying, pathophysiological abnormalities include accelerated gastric emptying, impaired gastric accommodation, and gastric or duodenal hypersensitivity to distention and nutrients. Novel treatments include tricyclic antidepressants in patients with normal gastric emptying, acotiamide (acetyl cholinesterase inhibitor) and 5-HT1A receptor agonists such as buspirone.

Rumination syndrome is characterized by repetitive regurgitation of gastric contents occurring within minutes after a meal. Episodes often persist for 1 to 2 hours after the meal, and the regurgitant consists of partially digested food that is recognizable in its taste. Regurgitation is typically effortless or preceded by a sensation of belching. Many patients report that no retching or nausea precedes the regurgitation. Patients then make a conscious decision to either re-swallow the food or spit it out. This has been summarized as a "meal in, meal out, day in, day out" behavior for weeks or months, which differentiates rumination from true gastroparesis which rarely occurs daily or with every meal. Patients often have a background of psychological disorder, secondary pain or a prior eating disorder. The history is usually sufficient, but the diagnosis may be confirmed by esophageal manometry and impedance measurements.
Strategies for prevention of gastric cancer: Progress from mass eradication trials

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IARC stated that approximately 89% of non-cardia gastric cancer are caused by *Helicobacter pylori* (*H. pylori*), and therefore, can be preventable by eradication of the organism [1]. To date, there have been reports on large-scale prevention trials targeting general population by eradication of *H. pylori* [2, 3], the results of which seemed to be promising. According to the trial in Taiwan, steady decline of the number of gastric cancer detected by annual endoscopic examination was shown in a relatively shorter period after eradication [3]. In the trial done in an area of high incidence of gastric cancer in China, however, the reduction of gastric cancer was not demonstrated at 7 years after eradication, but after 15 years, significant reduction of gastric cancer incidence was reported [2]. These differences may be related to the intensity and quality of endoscopic examinations, and to environmental conditions. Based on the data [2], a larger trial involving more than 180,000 subjects was started in China [4]. In Japan, conducting clinical trials to examine the eradication effects on gastric cancer prevention are difficult due to ethical problems. Instead, we promote nation-wide eradication by adopting health insurance coverage for eradication of *H. pylori* gastritis, enabling those who are infected can be treated. According to this policy, people identified as *H. pylori*-positive by health check, or outpatient clinic can receive eradication therapy after upper gastrointestinal examinations. Thus, this policy is to do primary and secondary prevention of gastric cancer in *H. pylori*-infected patients. Although there are no national registry data on this program, we estimated the number of patients who received eradication therapy using several indices. Our preliminary data clearly showed that the number of eradication therapy sharply increased after this new insurance policy was started 2 years ago. If the current trend of eradication continues, *H. pylori* infection in Japan would disappear in 20 to 30 years. Although it will take some time that this massive eradication leads to the reduction of gastric cancer mortality, we are looking forward to witnessing the decline of gastric cancer death in the next decade as a result of this “nation-wide” eradication program.

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Failed eradication of *Helicobacter pylori*: What should be done?

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Triple therapy using clarithromycin, amoxicillin and PPI was the worldwide standard treatment of *Helicobacter pylori* infection over two decades. However, the rate of success has decreased progressively over the years to an unacceptable level in many countries. Among the various possible reasons for this change, acquired resistance to clarithromycin is by far the major factor.

The best and most rational option after a first failure is to use a tailored therapy, *i.e.* to test clarithromycin susceptibility before prescribing drugs. This option is made possible not only by using culture and antibiograms but also by molecular methods because clarithromycin resistance is due to a few mutations (3) which arise in the target gene (23S rRNA) and are easy to detect. There are now real-time PCR methods which allow the detection of *H. pylori* and its eventual resistance to clarithromycin within a few hours, using either gastric biopsy specimens with a high sensitivity and specificity or in stools with a high specificity but low sensitivity. If the results still show a susceptible strain, other reasons for failure must be considered. If the strain is resistant, logically clarithromycin should be abandoned and a bismuth-based quadruple therapy favored. This combination has provided excellent results because it is not affected by metronidazole resistance and tetracycline resistance is virtually null.

There are still ways, however, to include clarithromycin in the combination by using the so-called sequential treatment. The rationale is to treat first with amoxicillin and PPI for 5 days which ensures a dramatic decrease in the bacterial load and therefore the resistant mutants, allowing a better chance to clarithromycin during the following 5 days. Others recommend concomitant or hybrid treatment where 3 antibiotics, including clarithromycin, are administered together; however, this implies the possibility that one of the drugs may not be effective and also increases the cost and adverse effects. These quadruple therapy options were proposed at the Maastricht IV Consensus Conference.

Recent data from the Far East have shown that a dual therapy amoxicillin-PPI may be the way to go. It was highlighted that amoxicillin should be prescribed 3–4 times a day instead of 2 in order to obtain a sufficient concentration at the gastric mucosal level during the 24 hours. Furthermore, a category of patients has been described as extensive PPI metabolizers linked to CYP2C19 enzyme and therefore are in need of a higher dose of PPI. Accordingly, a high dose of amoxicillin-PPI given 3–4 times a day may be the treatment of the future.
Helicobacter pylori is a bacterial carcinogen and incurs the highest known level of risk for the development of gastric cancer, a disease that claims hundreds of thousands of lives per year. Approximately 89% of the global gastric cancer burden and 5.5% of malignancies worldwide are attributable to H. pylori-induced inflammation and injury. However, only a fraction of colonized persons ever develop neoplasia, and disease risk involves well-choreographed interactions between pathogen and host, which are dependent upon strain-specific bacterial factors, host genotypic traits, and/or environmental conditions. These observations, in conjunction with evidence that carriage of certain strains is inversely related to esophageal adenocarcinoma and atopic diseases, underscore the importance of understanding mechanisms that regulate biological interactions of H. pylori with their hosts that promote carcinogenesis. One H. pylori strain-specific virulence determinant that augments the risk for gastric cancer is the cag pathogenicity island, a secretion system that injects the bacterial oncoprotein CagA into host cells. The longevity of intracellular CagA is prolonged in gastric stem cells due to inhibition of autophagy. However, H. pylori does not simply exist as a monoculture within the human stomach but instead, is a resident of a distinct gastric microbial ecosystem. While H. pylori is the dominant species, the presence of other microorganisms provides a genetic repository which may facilitate the generation of novel traits that influence gastric carcinogenesis. Host polymorphisms within genes that regulate immunity and oncogenesis also heighten the risk for gastric cancer, in conjunction with H. pylori strain-specific constituents. Further, environmental conditions such as iron deficiency and high salt intake can influence H. pylori phenotypes that lower the threshold for disease. Delineation of bacterial, host, and environmental mediators that augment gastric cancer risk has profound ramifications for both physicians and biomedical researchers as such findings will not only focus prevention approaches that target H. pylori-infected human populations at increased risk for stomach cancer, but will also provide mechanistic insights into inflammatory carcinomas that develop beyond the gastric niche.
Cholestatic and autoimmune liver diseases – From genetics to environment and back

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Genetic technologies have undergone rapid development over the last 25 years. The application of these technologies first led to the discovery of molecular pathways of bile formation and cholestasis through the elucidation of Mendelian traits by linkage analysis in affected families. Over the last 10 years, the application of a different genetic study design, 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. The lecture is intended to give an overview of these developments, with an emphasis on autoimmune cholestatic liver diseases, primary sclerosing cholangitis in particular. The overall picture is that of intertwined roles for genetic and environmental risk factors, and elucidation of genetic risk may guide the identification of critical environmental co-variables. In addition, there is evidence for shared pathophysiological pathways as the basis for the clinical co-occurrence of autoimmune diseases, liver and bile ducts no exception, yet recent modeling has delineated the genetic backbones for refined, molecular disease classifications of what appears to be mechanistically distinct disease conditions. Importantly, the genetic studies have opened for a collaborative working environment as a simple result of the large sample sizes required. This has led to the formation of disease specific consortia in cholestatic and autoimmune diseases with access to large patient cohorts, which are presently being explored for non-genetic stratifiers and molecular aberrations to delineate new treatment targets and future high precision, personalized medicine.
Session III

Pancreas
Decision making in necrotizing pancreatitis

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The management of acute necrotizing pancreatitis (ANP) has undergone a change of paradigms during the last two decades with a decreasing impact of surgical interventions, especially with regards to open necrosectomy [1].

Basically, modern ANP management is done conservatively as long as possible and therapeutic approaches aim at volume resuscitation, pain management and early enteral nutrition. The diagnostic gold standard of contrast-enhanced CT scan helps to evaluate the extent of necrosis of the pancreas which correlates with the risk of tissue infection [2].

The crucial point for decision making is the proven existence of infected pancreatic necrosis. This is achieved by diagnostic needle aspiration of the necrotic material and staining to prove bacterial and/or fungal infection [3]. In case of infected necrosis – besides calculated antimicrobial treatment – an interventional or surgical approach is required to prevent systemic septic progression of the disease. As the first step, percutaneous interventional drainage and spilling of the necrosis is preferable, in suitable situations, this can also be done by a transgastric intervention. In case of insufficient clearing of the infectious focus, a step-up approach must be considered, which implies a retroperitoneoscopic or transabdominal minimally-invasive necrosectomy and drain placement [4]. Postoperatively, a continuous lavage should be performed via these drains. In case of further deterioration of the patient or associated intraabdominal complications (e.g. bowel perforation or uncontrolled bleeding), an open surgical intervention must always be regarded as a salvage therapy. This approach offers the possibility to control complications and perform a further necrosectomy and extensive lavage for control of the focus. In contrast to historic approaches with staged re-laparotomies or an open-abdomen lavage postoperatively, today a continuous closed lavage via 2–4 intraoperatively placed drains should be the method of choice in this situation. However, associated morbidity (e.g. pancreatic fistula, fluid collections, pseudocysts) is about 50–60% and mortality up to 20% [5].

In summary, ANP is managed primarily by a conservative therapy. In case of proven infected necrosis, interventional and minimally-invasive approaches are the therapy of choice. Open surgery should be regarded as the last step for patients deteriorating despite other measures and should be postponed as long as possible, at least 3–4 weeks after onset of the disease.

References:


Development of pancreatic cancer: Targets for early detection and treatment

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Pancreatic cancer is currently the 4th leading cause of cancer death and projected to become the third leading cause of cancer-related death by 2030 due to delayed diagnosis and slow progress in treatment development [1]. The dismal prognosis of pancreatic cancer is caused by a variety of factors: a) Due to its location in the retroperitoneum pancreatic cancer causes symptoms only when it has already grown to an advanced stage and is no longer locally resectable [2]. b) Pancreatic cancer has a tendency to disseminate not only haematologically and to lymphatic tissue but also along nerve fibers, leading to an unusually high recurrence rate even after successful R0 resection [3]. For both of these issues a current consensus predicts that methods allowing earlier detection of pancreatic cancer may be of benefit [4]. c) Pancreatic cancer is highly resistant to chemotherapy, radiation therapy and even targeted therapy [5].

In the context of early detection methods and outside of imaging technologies very few biomarkers have been identified that could either distinguish pancreatic cancer from other disorders of the pancreas or detect it earlier than with currently available methods. The best established blood test for this purpose is carbohydrate antigen 19-9 (CA19-9), a Lewis antigen of the MUC1 protein-class. Unfortunately, CA19-9 can also be elevated in patients with nonmalignant diseases including liver cirrhosis, chronic pancreatitis, cholangitis as well as other gastrointestinal cancers [6]. CA19-9 has been reported to discriminate between pancreatic cancer patients and healthy controls (sensitivity 80.3%, 95% CI 77.7–82.6; specificity 80.2%, 95% CI 78.0–82.3) [7] and benign pancreatic disease (sensitivity 78.2%, 95% CI 72.3–80.4; specificity 82.8%) [8]. As CA19-9 is not expressed in Lewis blood type negative patients its sensitivity is limited to 92%, even under the best of circumstances. The fact that the distinction between cancer and chronic pancreatitis can be inaccurate in up to 1/3 of patients and that the negative predictive value of diagnostic assays is often no better than 50 to 60% [1], has prompted a search for alternative biomarkers. We have designed a study to investigate patients with suspected pancreatic cancer and have searched for metabolic biomarkers using a metabolomics approach (including lipidomics by MxP® Broad Profiling, MxP® Steroids and MxP® Lipids). We found that a distinct biomarker signature can distinguish pancreatic cancer from chronic pancreatitis with greater sensitivity and specificity (up to 91%) than CA19-9 and would improve the accuracy of the detection in 30% of patients compared to CA19-9. This is by far the largest trial (involving almost 1000 subjects) ever to investigate metabolomics biomarkers in the context of cancer and the results are very encouraging that such an approach may lead to an earlier detection of pancreatic cancer.

This issue of therapy resistance is harder to address. Some progress has been made over recent decades in identifying chemotherapy regimens that increase the overall survival of patients with pancreatic cancer. The most notable success was to establish that adjuvant chemotherapy in pancreatic and ampullary cancer can double the survival of patients after successful resection of the tumor [9, 10]. However, the
increase in survival after conventional chemotherapy regimens or after the introduction of targeted therapy approaches using either monospecific antibodies or tyrosine kinase inhibitors has only increased the survival from a median of 5 to 11 months. While this is statistically a significant increase it constitutes a much lesser treatment advance than achieved for patients with colorectal cancer or other solid tumors. A variety of structures have been targeted in pancreatic cancer such as the EGF receptor, the VEGF receptor, fibroblast activation protein α5β1-integrin, and others without resulting in a significant clinical benefit and neither overexpression of TNFα nor the use of broad spectrum receptor tyrosine kinase inhibitors have met the high expectations of patients and physicians. Since more than 90% of pancreatic cancer specimens carry somatic mutations in the oncogene k-ras this has turned into an attractive target. The disadvantage of the ras pathway is that it is vital for cellular survival in all tissues and not only cancer cells. This poses a number of difficulties for developing tumor specific anti-ras therapies. Other targets that are currently under investigation include polo-like kinase and heat shock protein 70, the latter of which appears to be involved in tumor cell resistance to apoptosis [11]. Once the appropriate target has been identified there remains the challenge how to deliver the compound to the tumor cells in a cancer that produces abundant extracellular matrix, an often severe impediment to drug delivery. To address this latter challenge a number of techniques included microspheres and albumin encapsulation of compounds have been invented. For the benefit of patients affected by this dismal disease much faster progress than achieved in the last decade would be required.

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Autoimmune pancreatitis: A riddle wrapped in an enigma

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Background: Only ten years ago, autoimmune pancreatitis (AIP) was rarely recognised as a clinical entity, at least in the West. Since then, studies globally, and international collaboration, has led to important advances in our understanding of its clinical features, disease course, and management, although the aetiopathogenesis of this curious disease remains to be fully elucidated.

Key Messages: Type 1 and type 2 AIP have been described, of which type 1 is the commonest form, and best defined. International consensus now recognises it as one of the many clinical manifestations of IgG4-related disease, and is now termed IgG4-related pancreatitis (IgG4RP). The disease is not confined to a particular race, gender, or age, but often presents after the fifth decade in men. A common presentation is with jaundice due to low bile duct obstruction related to diffuse pancreatic enlargement (historically often leading to a misdiagnosis of cancer). Acute pancreatitis is unusual. Other organ involvement is a particular feature, including biliary disease, retroperitoneal fibrosis, generalised lymphadenopathy, renal, and lung involvement. No single test makes the diagnosis, and diagnostic criteria for type 1 AIP/IgG4RP which incorporate clinical, laboratory, radiological, pathological, and therapeutic parameters should be applied. A particular attempt should be made to make a histological diagnosis, which is characterised by an IgG4+ve lymphoplasmacytic infiltrate. Management is not based on randomised studies, but corticosteroids are the mainstay of treatment, providing rapid clinical and radiological benefit. However, clinical relapse is common (particularly in type 1 AIP, and in those with associated other organ involvement). Additional immunosuppression may be required, including azathioprine, and rituximab may play an emerging role. The disease course is variable, but loss of organ function (especially pancreatic exocrine failure and pancreatic atrophy) may occur.

Conclusions: Significant advances have been made in our understanding and clinical recognition of AIP, such that fewer patients are now diagnosed following unnecessary surgery for presumed cancer. Clinician awareness of the disease, and the application of diagnostic criteria may allow prompt and effective treatment. Over the coming years we expect to gain a better understanding of the aetiopathogenesis of the disease, and optimal treatment regimens, aimed at not only treating the presenting episode (which is usually straightforward), but preventing organ dysfunction and disease progression.
Improving the outcome of acute pancreatitis: Current guidelines and beyond

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Acute pancreatitis is the most common indication for hospital admission in the US and its incidence is rising. In 2009 more than 270,000 patients were diagnosed with acute pancreatitis in the US and costs are estimated to exceed 2.5 billion dollars annually. Acute pancreatitis has a variable prognosis which is mainly dependent upon the development of persistent organ failure and infected necrotising pancreatitis. The latter is associated with a mortality rate of around 15%, while in the event of organ failure mortality exceeds 30%. Unfortunately, no drug therapy is available to ameliorate the disease course, in particular in patients with acute pancreatitis who develop a systemic inflammatory response syndrome (SIRS). In the past few years, based on large scale multi-centre randomised trials, some important novel insights regarding clinical management have emerged. Prophylactic administration of intravenous antibiotics does not prevent infected pancreatic necrosis. Antibiotics are only indicated in case of a proven infection or in case of a very strong clinical suspicion of either infected necrosis or cholangitis. In the latter case, biliary drainage is mandatory. A step-up approach of percutaneous catheter drainage followed by necrosectomy only when the patient does not improve, reduces new-onset organ failure and prevents the need for necrosectomy in about a third of patients with infected pancreatic necrosis (PANTER trial; ISRCTN13975868). A randomised pilot study comparing surgical to endoscopic necrosectomy in patients with infected necrotising pancreatitis showed a striking reduction of the pro-inflammatory response following endoscopic necrosectomy (PENGUIN trial ISRCTN07091918). These promising results have recently been tested in a large multi-centre randomised trial (TENSION trial; ISRCTN09186711) of which patient inclusion has been completed and results are eagerly awaited. Contrary to earlier data from uncontrolled studies, a large multi-centre randomised trial (PYTHON trial; ISRCTN18170985) comparing early (within 24 hours) nasoenteric tube feeding compared with an oral diet after 72 hours, did not show that the early nasoenteric tube feeding was superior in reducing the rate of infection or death in patients with acute pancreatitis at high risk for complications. Although early ERCP does not have role in the treatment of predicted mild pancreatitis, except in the case of concomitant cholangitis, it may ameliorate the disease process in patients with predicted severe pancreatitis. Currently a large scale randomized trial is underway to answer this important clinical question and results are expected in 2017.
Session IV

Systemic disorders and systemic approaches in the digestive tract
Gut and liver in vasculitic disorders

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Although the gastrointestinal tract including its related organs is not generally regarded as one of the primary organ systems of primary and secondary vasculitic disorders, there are numerous mechanisms of these diseases operative in or around the different structures and compartments of the GI tract. The majority of clinical symptoms and problems are linked to an alteration of (peri)vascular homeostasis. Alteration of perivascular matrix metabolism can also affect the functional integrity and motility of the GI tract. Aside the specific GI phenomena of the individual diseases as outlined in detail in the lecture, the epidemiology of GI involvement follows the characteristics of the respective underlying disease. In addition, gender and age do not influence the occurrence nor the severity of the GI manifestations significantly. With respect to clinical symptoms, vasculitides may result in abdominal pain, bleeding, ileus, intestinal necrosis and hematochezia because of reduced blood flow and hyper-acute occlusion in the antiphospholipid syndrome. Laboratory parameters can point to specific diseases but are frequently non-specific. Thus Doppler ultrasound, abdominal CT and angiography are required for identification and localization of the underlying disease. If fibrosis is more prominent than vasculitis as in systemic sclerosis, esophageal manifestations are most common, accompanied by dysmotility leading to reflux complicated by Barrett esophagus and potentially adenocarcinoma. Small-bowel involvement in fibrotic and vasculitic entities can cause pseudoobstruction obstruction, malabsorption and bacterial overgrowth. Therapeutic in vasculitides usually include corticosteroids and immunosuppressants, e.g., cyclophosphamide in granulomatosis with polyangiitis and in polyarteritis nodosa. In addition, anti-coagulation can be required in the anti-phospholipid syndrome. Virostatic drugs including interferon-α and ribavirin can be used in hepatitis B- and C-triggered vasculitides such as panarteritis nodosa and hepatitis C-associated cryoglobulinemia. Taken together, immediate steps of action need to be performed if vasculitis of the gastrointestinal tract is suspected to avoid irreversible damage to organs and life of the affected patient.
Gut and liver in sepsis

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Dysfunction of the gut and liver are frequent problems on the intensive care unit (ICU) during sepsis. The gut and the liver play a functional axis in normal physiology. In the gut digestion takes place and here bacteria are involved, which are present in the lumen of the bowel. During normal conditions the gut epithelium builds a physiological barrier for bacteria and thus in close proximity we have a sterile and a non-sterile compartment. However, nutrients are able to pass this barrier and reach the liver via the portal blood flow. In liver cells (hepatocytes) nutrients are metabolized in order to supply the whole body with the essential nutrients. Besides hepatocytes the liver also harbors a large non-parenchymal cell compartment consisting of Kupffer cells, hepatic stellate cells and endothelial cells. The interaction of these different cell compartments in the liver also provides a second line of defense, if bacteria or bacterial products pass the intestinal barrier and reach the systemic circulation. Here the different cells in the liver have different tasks. Especially Kupffer cells (local macrophages) are stimulated and secrete cytokines, chemokines and growth factors in order to activate other cells locally or to recruit additional immune cells into the liver leading to a systemic response. The immune mediators also have a direct impact on hepatocytes as they start to produce e.g. acute phase proteins, which are secreted in the circulation. Examples are C-reactive protein (CRP) or hepcidin the iron brake blocking the availability of iron for bacteria. However, hepatocytes also release bile acids as well as other essential components into the bile. They together reach the gut via the bile duct and through this also build an important feedback loop between liver and gut. Hence, changes in this closely controlled equilibrium have severe implications for body homeostasis.

Therefore, the gut-liver axis has different implications for and during sepsis. First it can be the essential source focus for providing a septic insult, e.g. by increased bacterial translocation in the case of an impaired intestinal barrier or when the bile flow is compromised via stones or tumors. Additionally, inflammatory foci can by the basis of sepsis derived from diverticula, the appendix or abscess in the liver. Besides of being the primary focus the gut and liver also react to septic insults and thus have an impact on the prognosis of the patients. These complications have to be taken into account, when treating patients in the ICU. Therefore, the gut and liver are essential predictors for the clinical picture of sepsis and these important aspects will be discussed in the presentation.
Five genetic disorders a gastroenterologist should know

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The role of germline genetic polymorphisms in gastrointestinal disease pathogenesis ranges from single-gene Mendelian disorders to common complex, multi-genic diseases. The large majority of genetic contribution to human disease is conferred through complex, typically polygenic disorders, for which inheritance of genetic factors confers increased susceptibility to disease, but is not determinative. Genome-wide association studies (GWAS) have identified thousands of such factors, providing enormous new insight into disease pathogenesis. However, these identified associations are typically of modest effects (i.e., odds ratios close to one), where the role of any single polymorphism is relatively modest in driving disease. At the other end of the spectrum, single-gene, Mendelian disorders represent only a small fraction human disease, but by their more determinative nature, can often provide insight into fundamental drivers of disease pathogenesis and human physiology. The advent of high throughput sequencing has made possible the systematic interrogation of less common, more private mutations. We will review five recent genetic advances that gastroenterologists should know about that provides particular insight into mechanisms of gastrointestinal disease with implications for medical practice: 1) major histocompatibility complex (MHC) role in pharmacogenetics, 2) ABO blood type polymorphisms and peptic ulcer disease, 3) advances in the genetics of eosinophilic esophagitis, 4) overlap between rare primary immune deficiencies and inflammatory bowel disease, and 5) overlap between the metabolic syndrome and fatty liver diseases.
Molecular imaging as a basis of treatment

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One of the major proceedings in endoscopy has been the advent of molecular imaging which possesses the potential to have a significant impact on existing diagnostic and therapeutic algorithms. Endoscopic molecular imaging enables visualization and characterization of mucosal lesions in vivo based on the molecular signature of individual cells rather than the morphological structure of the tissue. It can potentially be used to increase the contrast between normal and altered tissue for improved detection of malignant tissue in surveillance endoscopies.

Another highly attractive application for molecular imaging is the possible stratification of patients to respond to molecularly specific therapies prior to the initiation of the treatment. Anti-TNF antibodies are an approved and established treatment option in inducing and maintaining remission in Crohn’s disease patients. Nevertheless, about 50% of treated patients do not respond to treatment with the anti-TNF antibody. A central aspect in the management of these patients is therefore to identify potential responders to therapy before initiating the treatment. Reliable prediction of response to anti-TNF based therapies would enable a better selection of suitable patients for treatment beforehand, thus decreasing morbidity in patients with a low likelihood of response and enhance cost effective use of these treatment options. In view of current economic constraints in healthcare systems, the development of reliable predictors of response to these relatively expensive treatments is of central importance and might be essential to their future use.

As anti-tumor necrosis factor (TNF) antibodies suppress immune responses in Crohn’s disease patients by binding to membrane-bound TNF (mTNF) expressing mucosal cells, in vivo visualization of these cells via fluorescent anti-TNF antibodies was used to predict therapeutic efficacy of these agents. This approach is based on the assumption that there is a direct correlation between the expression levels of target molecules and the response to the associated biological therapy directed against it.

A Good Manufacturing Practice-conform fluorescent anti-TNF antibody was topically applied to the inflamed mucosa of Crohn’s disease patients and visualized using confocal laser endomicroscopy. It could be shown that patients with high amounts of mTNF positive cells showed significantly higher short-term response rates at week 12 (92%) after the initiation of anti-TNF therapy compared to patients with low amounts of mTNF positive cells (15%). It could moreover be shown that the clinical response was sustained over a follow-up period of one year. These data indicate for the first time that molecular imaging with fluorescent antibodies has the potential to predict therapeutic responses to biological treatment and open new avenues for personalized medicine by using fluorescent antibodies in Crohn’s disease.
Microbiota as therapeutic targets

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The inflammatory bowel diseases (IBDs) are among the most closely studied chronic inflammatory disorders that involve environmental, host genetic, and commensal microbial factors. This combination of features has made IBD both an appropriate and a high-priority platform for translatable research in host-microbiome interactions. Decades of epidemiology have identified environmental risk factors, although most mechanisms of action remain unexplained. The genetic architecture of IBD has been carefully dissected in multiple large populations, identifying several responsible host epithelial and immune pathways but without yet a complete systems-level explanation. Most recently, the commensal gut microbiota have been found to be both ecologically and functionally perturbed during the disease, but with as-yet-unexplained heterogeneity among IBD subtypes and individual patients. IBD thus represents perhaps the most comprehensive current model for understanding the human microbiome's role in complex inflammatory disease. In this presentation, we review the influences of the microbiota on IBD and its potential for translational medicine.
Session V

Small and large bowel
IBS: More than motility

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Most current treatment approaches in the management of the irritable bowel syndrome (IBS) focus on the predominant individual symptoms. Based on systematic reviews and meta-analyses, loperamide seems efficacious for diarrhea and isphagula for constipation, while musculotropic spasmolytics may relieve abdominal pain. Anti-depressants were found to be efficacious in meta-analyses, but their tolerance may be problematic and the therapeutic gain showed large variations between trials. A large number of studies have focused on probiotics, and although meta-analyses suggest efficacy of probiotics as a group, the magnitude of the therapeutic effect seems limited, the quality of the trials is often suboptimal and the type of probiotic studied is highly variable.

Lubiprostone, a chloride channel activator, was shown to be beneficial in chronic constipation and is also approved for treatment of IBS with constipation in the US. Linaclotide, a guanylyl cyclase-C agonist, which enhances colonic transit and chloride and fluid secretion through activation of the guanylin receptor, showed favorable effects on multiple symptoms in phase 3 studies in IBS with constipation. Eloflexibat, an ileal bile acid transport inhibitor, which promotes transit and bowel movements, is under evaluation in chronic constipation and tenapanor, a locally acting inhibitor of the intestinal sodium-hydrogen exchanger type 3, is being studied in IBS-C.

For IBS with diarrhea (IBS-D), the 5-HT3 receptor antagonist showed efficacy in both men and women, but is currently only approved in Japan. A multi-center study with the anti-emetic 5-HT3 receptor antagonist ondansetron showed efficacy on stool pattern in IBS-D. The poorly absorbable antibiotic rifaximin was shown to have efficacy in phase 3 trials in IBS without constipation. A recent retreatment trial evaluated the long-term response to rifaximin, and was the basis for FDA approval in IBS-D. The FDA also approved eluxadoline, is a mu/delta opioid antagonist which improved diarrhea, urgency and incontinence in IBS-D, but the drug was associated with increased occurrence of sphincter of Oddi spasm and biliary pancreatitis. Ibodutant is a tachykinin type 2 receptor antagonist, which showed excellent efficacy and tolerability in a placebo-controlled phase 2 study program in IBS with diarrhea. Phase 3 studies are ongoing.

The non-pharmacological treatment of IBS, with dietary interventions (mainly gluten elimination and low FODMAPs [fructose, oligo-, di-, monosaccharides and polyols]) has received a lot of attention lately. While responder rates vary across studies, perhaps based on regional variations in dietary intake of FODMAPs, the dietary approach seems to have acquired recognition as a valid therapeutic alternative. Long-term studies and comparative studies with pharmacotherapy, as well as elucidation of the underlying mechanisms of action, are needed.
Therapeutic approaches in IBD beyond the immunosuppressive paradigm

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We survive because we adapted to a world of microorganisms. All our epithelial surfaces participate in keeping up an effective barrier against microbes while not initiating ongoing inflammatory processes and risking collateral damage to the host. Major players in this scenario are antimicrobial peptides (AMPs). Such broad-spectrum innate antibiotics are in part produced by specialized cells but also widely sourced from all epithelia as well as circulating inflammatory cells. AMPs belong to an ancient defense system found in all organisms and participated in a preservative co-evolution with a complex microbiome. Particularly interesting interactions between host barrier and microbiota can be found in the gut. The intestinal cell lining not only has to maintain a tightly regulated homeostasis during its high-throughput regeneration, but also a balanced relationship towards an extreme number of mutualistic or commensal inhabitants. Recent research suggests that advancing our understanding of the circumstances of such balanced and sometimes imbalanced interactions between gut microbiota and host AMPs should have therapeutic implications for different intestinal disorders. Therapy could indirectly aim to bolster this system of antimicrobial defense or directly substitute for the lack of antimicrobial deficiencies. Of note both strategies would significantly alter the composition of the mucosal microbiome which might also be of interest in the therapy of metabolic diseases.
Targeted therapies in colon cancer today and tomorrow

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Colorectal cancer (CRC) is the third most common cancer type in western countries. Significant progress has been made in the last decade in the therapy of metastatic CRC (mCRC) with median OS of patients exceeding 30 months. The integration of biologic therapies with antiangiogenic or anti-EGFR monoclonal antibodies (mabs) in the treatment leads to significant progress in advanced noncurable disease. EGFR is a validated target for the mabs cetuximab and panitumumab leading to significant overall survival benefits when added to chemotherapy in patients with genomically selected all RAS wildtype mCRC.

After the Anti-VEGF mab bevacizumab the FDA approved ramucirumab the second antiangiogenic mab for the mCRC treatment after progression on a first-line bevacizumab-, oxaliplatin- and fluoropyrimidine-containing regimen.

Molecular heterogeneity of CRC has been recognized as pivotal in the evolution of clonal populations during anti-EGFR therapies and mutations in RAS genes predict a lack of response to anti-EGFR mabs. Mutations in the mitogen-activated protein kinase (MAPK)-phosphoinositide 3-kinase (PI3K) pathways like BRAF or PIK3CA mutations or HER2/ERBB2 or MET amplifications bypass EGFR signaling and also may confer resistance to anti-EGFR mabs.

The understanding of primary (de novo) and secondary (acquired) resistance to anti-EGFR therapies in mCRC and about predictive biomarkers is guiding the development of rational therapeutic strategies. Combination of targeted therapies are necessary to effectivly treat drug-resistant cancers. Combination therapy include pan-ERBB, MET or MEK inhibitors with anti-EGFR mabs in the first-line and refractory setting with promising results in early clinical trials.

HER2/ERBB2 amplification is a further driver of resistance to anti-EGFR mabs in mCRC patient-derived xenografts. HER2 Amplification for Colo-RectaL Cancer Enhanced Stratification (HERACLES), a phase II study of trastuzumab plus lapatinib or trastuzumab plus pertuzumab in HER2-amplified, KRAS exon 2 wild-type mCRC patients resistant to standard therapies, discovers that a dual HER2-targeted therapy may be a new option for HER2-positive mCRC.

Tumors with genetic defects in mismatch repair (MMR) harbor many more mutations than tumors without repair defects. A current study has shown that mismatch repair deficiency predicts responsiveness to immune checkpoint blockade with the anti-PD-1 immune checkpoint inhibitor pembrolizumab. The complete absence of objective responses in mismatch repair proficient tumors suggests that these patients should not receive anti-PD-1 antibody therapy. 85% of colorectal cancer patients are mismatch repair proficient.
Endoscopy beyond visible light as basis of treatment

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White light endoscopy (WLE) is the diagnostic basis for diseases within the luminal gastrointestinal tract. It visualizes the disease, allows tissue sampling, and effective treatment of complications. WLE has been further enhanced by the integration of high definition into currently available endoscopes, and may be augmented by dye spraying (chromoendoscopy) or narrowing of the incident light (NBI) or post image acquisition processing (i-scan, FICE, SPICE; virtual chromoendoscopy). While these WLE techniques are outside the scope of this review, every novel technique has to compete against this high standard, i.e. has to provide an additional benefit for the patient. Such novel endoscopic approaches include wide field techniques to visualize and enhance large areas, and point techniques which image a small area at ultrahigh resolution. While the former are primarily used for detection of suspicious lesions within the GI tract, the latter are utilized to exactly characterize a lesion, for example prior to endoscopic therapy. In addition, a completely novel approach uses probes for risk stratification of patients by monitoring distant mucosal alteration associated with field cancerization.

Non-WLE imaging can be based on superficial structural alterations, functional abnormalities, changes in the molecular composition, and/or changes in perfusion. Autofluorescence imaging, confocal laser endomicroscopy (CLE) and non-linear optical imaging, optical coherence tomography (“microendoscopy”), Laser induced fluorescence spectroscopy and Raman spectroscopy, elastic light-scattering fingerprinting, low-coherence enhanced backscattering and others are techniques that are used for detection and characterization of lesions. While the some techniques have been thoroughly evaluated in clinical trials, most are still under investigation.

The extent to which an additional benefit to the patient can be provided by novel technologies, naturally differs between different indications. For example, WLE polyp characterization in the colon during screening colonoscopy is quite reliable. Here, additional technologies have to yield excellent results in order to be better than the current WLE gold standard, in order to be able to discard a polyp after resection or to even leave it in place. In contrast, for early detection of pancreatic cancer, every novel technique is highly welcome and meets an urgent clinical need due to the lack of a current gold standard. First attempts to use measurement in the duodenal mucosa for this aim are promising. Imaging with CLE to visualize the impaired mucosal barrier function in inflammatory bowel diseases is predictive of recurrent flares. This may be used for risk stratification of patients and for monitoring of response to medical therapy.

In summary, advanced imaging during endoscopy beyond WLE has become a vivid field of ongoing research, and first translations into clinical practice have been achieved in recent years. While WLE is still the standard of care, first indications show the additional impact of these novel techniques.
Building a better human intestine

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As the gastrointestinal system is required for absorption and digestion of nutrients as well as the most common site for absorption of numerous medications, models to understand rare and common human diseases are crucial yet lacking. As many diseases are not applicable to animal models, human studies are currently required to test therapies. Development of functional and specific human intestinal tissue would address this major gap by providing: 1. A means to screen specific factors associated with drug and nutrient absorption in healthy intestine. 2. Unlimited access to disease-modeled specific tissue to support studies characterizing common and rare GI diseases. 3. Development of therapies focused on treatment of specific common (including infectious diseases (viral and bacterial) and rare (cystic fibrosis, IBD, celiac) diseases. Our group has recently described robust and efficient methods for directing human pluripotent stem cells (hPSCs) and induced pluripotent stem cells (iPSCs) into an intestinal 3D culture system; that when transplanted efficiently develop into functional human small intestine (Watson et al. Nature Med. 2014). Our ongoing studies support the reproducible phenotype over numerous grafts generated from the same human pluripotent stem cell line. Ongoing advances in the model have provided a way to transplant the grafts into the intestinal mesentery that can be incorporated into the lumenal stream of the mouse. In addition, recent data support our ability to generate a human intestine with an ENS. Efficient expansion of iPS cells towards functional human intestine will provided potentially unlimited access to growing this tissue to develop human specific assays. Initially focusing on our patients with identified GI diseases.
Session VI

Liver and biliary system
**FXR agonists for liver disease**

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Besides their well-established roles in dietary lipid absorption and cholesterol homeostasis, bile acids (BAs) act as signalling molecules with hormonal actions mediated through activation of dedicated BA receptors such as the nuclear BA receptor farnesoid X receptor (FXR: NR1H4) and the membrane-bound BA receptor TGR5 (also called GPRBAR1 or M-BAR/BG37). Besides FXR and TGR5, BAs are able to activate other nuclear receptors (NRs) such as pregnane X receptor and vitamin D receptor. Ligand-activated NRs such as FXR control a broad range of metabolic processes including hepatic BA transport and metabolism, lipid and glucose metabolism, drug disposition, as well as liver regeneration, inflammation, fibrosis, cell differentiation and tumour formation. Moreover, FXR has anti-inflammatory and immunomodulatory actions and controls intestinal permeability as well as gut microbiota. Conversely, gut microbiota metabolize BAs (with formation of secondary BAs) which in turn modulates BA signalling. In addition to naturally occurring ligands, FXR and other NRs can be targeted by recently developed therapeutic drugs which opens important perspectives for pharmacotherapy of cholestatic and metabolic liver disorders, including the complications of liver cirrhosis such as portal hypertension and hepatocellular cancer (HCC).

Notably, UDCA (and its derivative norUDCA) is not a ligand for FXR or TGR5 and exerts its therapeutic effects via other, largely post-transcriptional mechanisms. Recent data suggest, that high-dose UDCA may even have FXR-antagonistic actions in vivo in humans. A range of steroidal BA-derived and non-steroidal FXR ligands has been tested in preclinical models of cholestatic and metabolic liver diseases, liver fibrosis, portal hypertension, HCC and a few already undergo clinical testing for some of these indications. Notably, some of these ligands have dual FXR and TGR5 activity. In addition to systemic ligands, gut-selective FXR ligands have been tested which may exert metabolic actions via stimulation of intestinal fibroblast growth factor (FGF)-15/19 production. As complementary approach also targeting FXR-downstream signaling, direct FGF-19 mimetics have been developed for treatment of cholestatic and metabolic liver diseases.

Among clinically tested FXR agonists, most data are so far available for obeticholic acid (OCA; also known as 6α-ethyl-chenodeoxycholic acid or previously as INT-747), which has been clinically tested in PBC, NASH and portal hypertension. As such OCA improved biochemical parameters of cholestasis in PBC patients not responding to (or not tolerating) UDCA. In line with the results obtained with combination therapy with UDCA in non-responders, OCA monotherapy also achieved a significant reduction of cholestasis in treatment naive PBC patients. Dose-dependent pruritus was the most common adverse event in patients receiving higher doses of OCA. OCA is currently also tested in PSC in a U.S trial. While targeting concomitant inflammatory bowel disease by FXR may be an attractive concept in PSC, some concerns have been raised regarding potential carcinogenic effects of FXR-stimulated FGF-19 in these patients who are at high risk for malignancy.
A pilot study with the OCA in type 2 diabetic with NAFLD showed improvement of liver function tests and hepatic as well as peripheral insulin sensitivity (clamp studies). A larger placebo-controlled study (FLINT trial) with 283 NASH patients randomised to either 25 mg OCA or placebo for 72 weeks has recently been completed. The primary endpoint was an improvement of liver histology defined as a decrease of NAFLD activity score (NAS) ≥ 2 points which was accomplished already at interim analysis which led to premature stop of the trial. Moreover, OCA treated patients showed even a significant reduction in fibrosis compared to placebo. In contrast to the pilot study, insulin sensitivity (assessed by HOMA index) deteriorated compared to placebo. Pruritus, a side effect already seen in studies with PBC, was also observed with OCA in NASH, although to a lesser degree. Moreover, patients treated with OCA showed an increase of LDL and a decrease of HDL despite concomitant anti-lipidemic drugs in 50% of the patients. Long-term follow up data are needed to evaluate the impact of FXR ligands on cardiovascular risk in NAFLD/NASH.

Interestingly, OCA has been shown to reduce portal pressure in preclinical models and patients with liver cirrhosis and may also play a key role in maintaining gut integrity. Loss of FXR signalling has been linked to hepatic carcinogenesis, while FXR ligands protect from HCC development in preclinical mouse models. One of the concerns of FXR therapy may be stimulation of tumour development via FGF15/19; a recently developed FGF-19 mimetic apparently lacks these potentially carcinogenic properties. In summary, the broad immunometabolic actions of FXR ligands hold considerable promise for treatment of a wide range of metabolic and cholestatic liver diseases, perhaps even including complications of endstage liver disease such as portal hypertension and HCC development.

References (further reading):

Following chronic liver injury of any etiology, there is progressive fibrosis. To date, removing the causative agent is the only effective therapy to stop or even reverse liver fibrosis. Therefore, the development of effective antifibrotic therapies represents a challenge for modern hepatology. In the past decade, dramatic advances have been made in the understanding of the cellular and molecular mechanisms underlying liver fibrogenesis, which have identified new targets for therapy.

The identification of activated hepatic stellate cells (HSCs) as the major fibrogenic cell type in the injured liver, as well as the recognition of key cytokines involved in this process, have facilitated the design of promising new antifibrotic therapies. These therapies are aimed at inhibiting the accumulation of activated HSCs at the sites of liver injury and preventing the deposition of extracellular matrix. Although many of these approaches are effective in experimental models of liver fibrosis, their efficacy and safety in humans are still unknown. This lecture describes the current therapeutic approaches for liver fibrosis and discusses different features of activated HSCs as a target to design new treatments to inhibit scar formation in chronic liver diseases.

A number of antifibrogenic agents are effective in cultures of activated HSCs and in experimental models of liver fibrosis. Importantly, clinical trials evaluating the efficacy and safety of some of these agents are underway. The most promising therapies include antioxidant drugs, cytokine modulators, and antagonists of vasoconstrictor substances. Moreover, several natural products show antifibrotic activity in experimental fibrosis. Future research should be focused on the pathogenesis of fibrosis in different types of liver diseases as well as on the development of drug carriers to specifically deliver antifibrotic compounds to the activated HSCs.
Treatment of hepatocellular carcinoma

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While years ago the treatment options for hepatocellular carcinoma (HCC) were almost limited to surgical resection. In addition, diagnosis was frequently established at an advanced stage when patients presented cancer related symptoms and significant liver function impairment. Better awareness of the incidence of HCC in cirrhotic patients and the capacity to detect and diagnose it at an early asymptomatic stage have sharply changed the clinical scenario. Indeed, several options have now been incorporated into the treatment armamentarium and robust evidence has allowed defining the optimal treatment approach in clinical practice guidelines by scientific associations.

The stratification of the patients according to evolutionary stage, prognosis and treatment allocation is widely done following the BCLC staging and treatment model. This combines the evaluation of tumor burden, liver function and health status, and links each of its five stages into an initial treatment alternative. Obviously, this first evaluation approach has to be fine tuned according to the specific profile of the individual patient so that the treatment decision is finally taken as per a personalized evaluation.

Current treatment options with positive impact in survival if applied in the adequate candidates include surgical resection, transplantation, ablation, chemoembolization and sorafenib. Radioembolization has significant antitumoral activity but data about impact in survival are eagerly awaited. Finally, better knowledge of the molecular events driving oncogenesis and tumor progression should ultimately identify new therapeutic targets and prime a treatment decision based in biology rather in mere tumor size and number as currently done.

References:

State-of-the-Art Lecture

Hepatology after hepatitis C

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The ~90% probability of curing individual patients with hepatitis C using direct-acting antivirals represents one of the most dramatic medical success stories of the modern era, and the journey from viral discovery to treatment occurred over just ~25 years. The realities of the global burden of disease (2–3% of the world’s population is infected), limited access to care and cost of treatment means that hepatitis C will continue to be a major problem for 25 years to come. But what if hepatitis C (and hepatitis B) could be eradicated? Since liver transplantation and hepatitis C management have been the mainstays of academic hepatology practice, where do we go from here? Unfortunately, we are in an era where the incidence and prevalence of liver diseases around the globe is increasing, and death from complications of cirrhosis is now amongst the top 10 causes in most countries so there will continue to be a role for hepatologists in the future. Despite remarkable progress, success at the population level is limited by the resource-intensive nature of caring for patients with end-stage disease. Accordingly, the major advances in the next decade are likely to focus on i) earlier identification of individuals and populations at higher risk for liver diseases, and ii) initiation in high risk populations of specific strategies for early detection and treatment of fibrosis, cancer and cirrhosis. The answers will lie in large part in the further exploration of the human genome in carefully phenotyped patients. Risk variants in the PNPLA3 gene represent the best example to date. The risk variants are common and are enriched in certain populations around the globe; and individuals that possess risk variants are more likely to have liver injury from fatty liver disease (even as children), alcohol, and viral hepatitis. Further, those with liver injury are more likely to progress to cirrhosis and hepatoma. Similarly, in those with established liver disease, use of biomarkers and other strategies for early detection of fibrosis and hepatoma will pay dividends as the next generation of treatments focusing on i) anti-fibrotic strategies and ii) liver regeneration move to the forefront. Alas, there remains an important need to invest in hepatology as a growth industry even after the (unlikely) demise of hepatitis C.
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POSTER ABSTRACTS

Poster Numbers 1 – 106

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Serotonin: A marker for the diagnosis of hepatocellular carcinoma in cirrhotic patients?

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Hepatocellular carcinoma (HCC) is the third most frequent cause of cancer mortality among men worldwide. Serotonin is a biogenic amine and ligand in a family of 5-HT receptors with a diverse range of serotonergic actions. The majority of serotonin in the body (90%) is synthesized by enterochromaffin cells of the gastrointestinal tract and is transported to various sites. Serotonin regulates blood flow and vascular tone on a portal and sinusoidal level, stimulates mitogen for hepatocytes and promotes liver regeneration. 5-HT has emerged as a mediator of different pathological conditions (double-edged sword). It contributes to liver fibrosis, mediates oxidative stress in non-alcoholic steatohepatitis and aggravates viral hepatitis. These conditions play a role in the tumorigenesis of hepatocellular carcinoma (HCC). Impaired metabolic function in liver cirrhosis and slow uptake and storage of serotonin by the platelets are sequelae of kinetic changes in serotonin transport mechanisms or abnormal serotonin release from dense granules of activated platelets (platelet exhaustion), and contribute to elevated plasma serotonin levels, which may facilitate tumor growth in primary liver hepatocellular carcinoma.

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

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

Results: Plasma serotonin was significantly higher in the group with cirrhosis with a median level of 119.4 ng/ml compared with the control group, which had a median value of 51.5 ng/ml (p < 0.001). Furthermore, a significant difference was found between the cirrhosis and HCC group, which had a median value of 478.35 ng/ml, and the control group and cirrhosis group (p < 0.001).

Conclusion: Plasma serotonin levels were significantly higher in patients with cirrhosis and HCC than in those with cirrhosis only, and played a role in the tumorigenesis of hepatocellular carcinoma.
Malnutrition prevalence among patients with liver cirrhosis in relation to the duration of cirrhosis history

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Introduction: Protein calorie malnutrition is associated with an increased risk of morbidity and mortality in patients with cirrhosis and occurs in 50–90% of these patients. The aim of this study was to evaluate the prevalence and severity of malnutrition in hospitalized cirrhotic patients depending on the duration of cirrhosis history.

Methods: Malnutrition was investigated in 164 (age 51.33 ± 11.25 years, 59% male, 70% alcohol) patients with liver cirrhosis by applying biological and anthropometric parameters in the total group and the groups in relation to the duration of cirrhosis history. According to medical history the patients were divided in 3 groups: group 1 – with medical history < 12 months, group 2 – 12–59 months; group 3 > 60 months.

Results: Prevalence of malnutrition in cirrhotic patients was 114/164 (89%). Malnutrition occurred in patients with the short history of cirrhosis compared to other groups more often, but the differences were not significant (92.2%/86.3%/70%; χ² = 5.184, P = 0.075). Analysis of malnutrition severity showed that about 50% patients in every group had mild disorder of the nutritional status. Severe malnutrition occurred more rarely in total group, but significantly more frequently in group 3 compared to group 1 (14.3%/2.1%; χ² = 7.751, P = 0.021).

Discussion/Conclusion: Malnutrition is prevalent among patients with liver cirrhosis and occurs more frequently in cirrhotic patients with the short cirrhosis history. Malnutrition severity increases significantly depending on the cirrhosis duration.
Evaluation of the *Lavandula stoechas* L. extract in the experimental model of irritable bowel syndrome induced by acetic acid

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**Introduction:** Irritable bowel syndrome (IBS) is a high prevalent functional gut disorder. Nowadays, its pharmacological treatments have unsatisfactory effects. For this reason, there is an increasing interest for complementary medicine. The aim of the study was to evaluate the effects of *Lavandula stoechas* L. extract in an experimental model of irritable bowel syndrome (IBS) in rats induced by intracolonic instillation of acetic acid. *Lavandula stoechas* extract was able to reduce the visceral hypersensitivity as well as to improve the altered immune response clearly involved in IBS.

**Methods:** Female Wistar rats (300–320 g) were administered 2% acetic acid, 3 days after they were divided into three different treated experimental group (n = 10), which received orally the extract at 1, 10 and 25 mg/kg; a non IBS and an untreated control IBS group. Ten days later, abdominal withdrawal reflex to colorectal distension (CRD) was semiquantitatively scored and referred pain with von Frey filaments was evaluated.

**Results:** The IBS control group showed higher values in comparison with non-IBS group. The treated rats with 25 mg/kg of *Lavandula stoechas* extract showed reduced CRD score values and the referred pain than IBS control. Also the treated group with *Lavandula stoechas* extract at 1 mg/kg was able to decrease the referred pain. When the rats were sacrificed, the expression of different markers was evaluated in the colonic tissue by qPCR. The results revealed that *Lavandula stoechas* extract was able to alter the expression of COX-2 and toll like receptors. In addition, the extract was also able to restore the reduced expression of the mucins. *Lavandula stoechas* extract was able to reduce the visceral hypersensitivity as well as to improve the altered immune response clearly involved in IBS.

**Discussion/Conclusion:** *Lavandula stoechas* extract was able to reduce the visceral hypersensitivity as well as to improve the altered immune response clearly involved in IBS.
Single-centre clinical experience of Hemospray endotherapy in patients with acute upper gastrointestinal bleeding

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Introduction: Acute upper gastrointestinal bleeding (AUGIB) is a common medical emergency associated with a hospital mortality of 10%. Therapeutic endoscopy with conventional combined injection and mechanical application is the recognised 1st-line intervention to achieve haemostasis. However, 5–10% of patients experience recurrence of bleeding after initial endoscopic haemostasis. Hemospray (TC-325; Cook Medical, Winston-Salem, USA) endotherapy is now becoming widely available as a novel agent to augment hemostatic efficacy. We report on the ‘real-life’ single-centre experience in the UK, of the efficacy and safety of Hemospray in the management of AUGIB.

Methods: A single-centre retrospective analysis of all patients treated with Hemospray from September 2013 to April 2015 was performed. Case notes were reviewed and data collected including demographics, Rockall score, endoscopic modality, length of hospital stay, repeat procedures and transfusion requirements.

Results: 58 patients (42 male) with a mean age of 64.7 years (range 26–92) were treated with Hemospray at endoscopy. The indications for endoscopy were melaena (29, 50%), profound anaemia (16, 28%), haematemesis (6, 10%), oesophagogastric varices (5, 8.6%), dysphagia (1, 1.7%), dyspepsia (1, 1.7%). The mean pre-endoscopy Rockall score was 3 (range 0–7), post-endoscopy Rockall score 5 (range 1–10). Hemospray was applied as the single modality in 16 cases (2 oesophageal tumours, 4 gastric tumours, 4 peptic ulcers, 1 peptic stricture, 1 Dieulafoy lesion, 1 unidentified D2 bleeding source). Adjunctive modality occurred in 31 cases (54.8% following variceal band ligation as the primary modality). 11 cases required rescue therapy (10 peptic ulcers, 1 polyp bleeding). Successful haemostasis with Hemospray was achieved for all but one patient (98.3%). This patient (Dieulafoy lesion with Hemospray as solitary modality) required repeat endoscopic dual therapy (adrenaline/clips). 2 cases of bleeding DU required Hemospray despite radiologic embolization of oozing visible vessels. No procedural complications during and immediately post-application were reported. There were no treatment-related adverse events. There was one in-patient death, not attributable to AUGIB/endoscopy. The mean length of hospital stay was 12 days (range 1–51).

Discussion/Conclusion: Our experience confirms Hemospray to be an effective endoscopic modality for achieving successful haemostasis in the vast majority of cases of AUGIB, when used as single, adjunctive, or rescue endotherapy, for a wide-range of causes for AUGIB. Our ‘real life’ single-centre UK experience supports Hemospray for all major causes of AUGIB; a modality that is easy to apply, and safe to use.
Development and validation of a new disease severity index: The inflammatory bowel disease index (IBDex©)

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

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

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

Discussion/Conclusion: IBDex© is the first properly validated clinical disease severity index in IBD. Our results showed that it is valid, reliable and reproducible and has the potential to be used in clinical practice.
The Crohn’s and ulcerative colitis questionnaire-12 (CUCQ-12): A short quality of life tool for inflammatory bowel disease

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Introduction: There are currently no established, disease-specific quality of life (QoL) measures for inflammatory bowel disease (IBD) that are used routinely in clinical practice. Existing tools are often lengthy, time consuming and not applicable to all patients with IBD. The Crohn’s and ulcerative colitis questionnaire (CUCQ-32) has been recently developed and validated to assess patient QoL in IBD. However, a shorter and simpler form is needed for application in routine clinical practice. The aim of this study was to derive and validate a shorter form of the CUCQ-32.

Methods: A shorter form of CUCQ-32 was derived by stepwise regression to select the questions that best explain the variance in the CUCQ-32 scores. Construct validity was carried out using the EuroQol 5 dimensions (EQ5D) questionnaire 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 during their second follow up visits.

Results: Using the data from 124 patients with acute UC, a 12 item questionnaire (CUCQ-12) was developed using stepwise regression. The validity and reliability of the CUCQ-12 was examined using data from 484 different patients with IBD who completed the CUCQ-12. The CUCQ-12 demonstrated good internal consistency (Cronbach’s $\alpha = 0.864$); had good reproducibility (intra-class correlation coefficient = 0.743); was well correlated with the EQ5D ($r = -0.484$), HBI ($r = 0.452$) and SCCAI ($r = 0.427$); and had good responsiveness statistics (details).

Discussion/Conclusion: CUCQ-12 was proven to be a valid and reliable tool for assessing the QoL of patients with IBD. This short questionnaire could be applied routinely in clinical practice.
Comparison of affective temperament profile between patients with irritable bowel syndrome and healthy controls

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Introduction: Irritable bowel syndrome (IBS) is the most common functional disorder of the gastrointestinal tract, which is characterized by abdominal pain and changes in bowel habits. However, etiopathogenesis of IBS still remains unclear. Several studies indicated high rates of psychiatric comorbidity among patients with IBS and psychotropic drugs, particularly antidepressants, were reported to be effective for the treatment. On the other hand, affective temperament is a stable trait variable that shows the automatic emotional response to events as establishing individual’s activity level, rhythms, mood and related cognitions. There is a strong body of evidence showing that temperament constitutes the basis classical mood and anxiety disorders and higher affective temperament scores indicate a vulnerability to these psychiatric disorders. With this background, we aimed to compare affective temperament scores of IBS patients with healthy controls to study temperament as a predictor of mood and anxiety disorders.

Methods: We recruited 23 patients diagnosed with IBS according to ROME III criteria and 23 healthy controls. Patients with any chronic diseases (liver, renal, heart, inflammatory and rheumatological diseases, and other systemic diseases such as pulmonary diseases, anemia, hematological disease) and alarm symptoms (weight loss, anemia, hematochezia) were excluded from the study. All patients and healthy controls were agreed to participate to the study and signed written informed consent in accordance with the Declaration of Helsinki. TEMPS-A scale to evaluate affective temperament profile of the participants. SPSS software (Version 19.0; IBM, Armonk, NY) was used for statistical analysis. Normality of distribution in the groups was assessed using the Kolmogorov-Smirnov test. Differences between groups were evaluated using Student’s t and chi-square tests; p < 0.05 was considered statistically significant.

Results: There was no difference between patient and control groups in terms of age (p = 0.40, t = -0.86) and gender (p = 0.13, χ² = 2.24). When we compared temperament scores between groups, patients with IBS had higher depressive (p = 0.007, t = -2.82), cyclothymic (p ≤ 0.001, t = -5.14) and anxious (p ≤ 0.001, t = -4.49) scores than healthy controls. Hyperthymic (p = 0.79, t = -0.27) and irritable (p = 0.55, t = -0.60) temperament scores were similar between groups.

Discussion/Conclusion: Higher depressive, cyclothymic and anxious temperament scores in IBS group than healthy controls indicate the vulnerability of these patients to mood and anxiety disorders considering that affective temperament is subclinical form of mood and anxiety disorders. IBS patients are more likely to represent a higher frequency of outpatient visits and mood-anxiety symptoms worsen the clinical course and quality of life. Thus, establishing the affective temperament properties in IBS patients may help clinicians to predict the risky group of patients for depressive and
anxiety disorders. On the other hand, similar irritable temperament scores between patient and control groups might be related with relatively small sample size of the study. Our study is the first to evaluate the affective temperamental features of women with IBS. Further studies with a bigger sample size and longitudinal design is required to clarify the relation between affective temperament and psychiatric conditions in IBS.

References:

Two-week protein-enriched low-calorie diet (HEPAFAST) shows rapid improvement of fatty liver as assessed by controlled attenuation parameter

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Introduction: Fatty liver (FL) is one of the most prevalent liver disorders increasing the risk of fibrosis and cirrhosis. FL occurs frequently in patients with diabetes. The aim herein was to assess for therapeutic effects of a short-term dietary intervention on FL, as quantified using the controlled attenuation parameter (CAP) during transient elastography.

Methods: Sixty-six patients with FL received a 14-day low-calorie liver-specific diet containing 800 kcal/day (HEPAFAST: 41% protein, 29% carbohydrates, 24% fat, 6% fiber) and a maximum of 200 kcal/day through vegetable intake. The following parameters were assessed pre- and post-intervention: liver fat contents using the CAP algorithm; body composition; serum liver function tests and lipids.

Results: All 66 patients (age 56 years [25–78], 52% women, BMI 31.7 kg/m² [22.4–46.3]) successfully completed the study. A significant reduction in FL (14.3%; P < 0.001) was observed after only 2 weeks; median CAP score decreased from 296 dB/m (177–400) to 264 dB/m (100–353). Simultaneously, BMI decreased by 5%, 32% of the patients were reclassified into a lower BMI category, and body fat and visceral fat contents decreased by 7%. Serum triglyceride, LDL and GGT also decreased (all P < 0.001). Interestingly, 11 patients (73% women) demonstrated a CAP increase despite improvements in body composition, thus were classified as hepatic non-responders. A subgroup analysis of the responders revealed a decrease of 17% in median CAP scores from 311 to 263 dB/m. When comparing diabetics with non-diabetics (24% vs. 76%), equal improvements of liver fat, body composition, serum liver function tests and lipid profiles were observed (all P > 0.05).

Discussion/Conclusion: This non-invasive elastography-based study demonstrates for the first time improvements in liver fat, as quantified by CAP, after a short-term protein-enriched low-calorie diet. The dietary intervention reduced body weight and improved body and liver composition in diabetics and non-diabetics alike.
Primary colon involvement in non-Hodgkin lymphomas

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Introduction: The gastrointestinal (GI) tract is the predominant site of extranodal non-Hodgkin lymphomas (NHLs). Primary NHLs of the GI tract is rare, but the secondary GI involvement is relatively common.

Methods: Our study aims to assess the incidence of primary and secondary involvement of the colon in the NHL. Endoscopic evaluation is an ideal way for verifying the extension and also for the collection of biopsy material.

Results: Between 2000 and 2013 our department has collected 1056 NHL (except: CLL, hairy cell leukemia and mycosis fungoides). Of the 22 NHL (2.08%) with primary gastrointestinal lymphoma, 14 (63.63%) had gastric involvement and only 4 (0.37% from all lymphomas) had colorectal lesions, 1 of the cases presented multiple lesions (gastric and colonic). Immunohistology was concordant with MALT in 2 patients and 1 case with large B cells and 1 case with mantle lymphoma. Endoscopic appearance was nodular lesions ulcerated in 1 case and infiltrative in other.

At diagnosis, secondary lymphoma involvement to the digestive tract were seen in 68 (6.43%) of patients, with only 11 with colon lesions (1.04% for all lymphoma and 16.17% from all gastrointestinal secondary lymphoma involvement).

Histological, 3 cases were Burkitt-like, 4 mantle cell lymphoma, 2 large cell lymphoma, 3 follicular lymphoma. Four cases had active HIV infection (3 Burkitt and 1 large cell lymphoma).

Endoscopic appearance was nodular and nodular ulcerative lesions in 8 cases, the other 3 cases were infiltrative appearance, 2 of them presenting also ulcerative lesions. Colorectal lymphoma may present with abdominal pain 5 (45.45%), overt or occult bleeding 5 (45.45%), diarrhea 3 (27.27%) or rarely, bowel obstruction (9.09%). Therapeutic approach included surgical resection, radiotherapy and chemotherapy compared to histology, stage and biological status of the patient.

Discussion/Conclusion: Our study confirms the rarity of primary involvement of colon by lymphoma lesions. Secondary colonic lesions are more common, predominant histology were Burkitt-like/large cell (HIV+) and mantle cell lymphoma.
Therapeutic approach in primary indolent gastrointestinal lymphoma

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Introduction: Primary gastrointestinal NHLs are rare lesions and their optimal treatments have not been defined. The treatment of gastrointestinal extranodal marginal zone B-cell lymphoma of MALT type is dictated primarily by stage and histologic grade.

Methods: From 1995 to 2013, there were registered 26 lesions of indolent lymphoma with primary gastric localization.

Results: From the 15 cases with E-MZL gastric, 6 (40%) present themselves in localized stage, IE, IIE. Five of these ones (83.33%) responded the Helicobacter pylori (HP) eradication therapy. In evolution, 2 patients relapsed, 1 locally and the other systemic. Both cases responded to CVP chemotherapy, the estimated survival rate of 5 years being 100%. Five patients (33.33%) presented with an advanced stage of the disease (III and IV), 20% has laparotomy for diagnostic/treatment reason, with partial gastric resection. Three of the 5 of advanced stage patients underwent eradication therapy for HP, but only 1 patient presented a partial response. A whole lot of patients who was in an advanced stage were treated with protocols of CVP or CHOP type by rapport of the presence of confluent clusters or sheets of large cells resembling centroblasts. The rate of response was 80%. Three of these patients presented multiple relapses, controlled by chemotherapy. The estimated survival rate of 5 years in this lot has been of 60%. For follicular lymphoma 26.92% (7 patients) the treatment was R-CHOP or R-FC with rapid favorable evolution and the same as first line therapy for mantle cell lymphoma 15.38% (4 patients).

Discussion/Conclusion: The E-MZL therapy presents characteristics through the response to the HP eradication therapy. For other type of gastric indolent B lymphoma mainly in advanced stage the first line therapy was polychemotherapy. The evolution and therapy of these lymphoproliferative lesions, besides these characteristics, is similar to the malignant indolent lymphomas.
Loss of integrin β₆ (ITGB6) protects from colon cancer development *in vivo*

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Introduction: Each 4th colorectal cancer (CRC) patient develops metastatic disease. A central process in metastatic CRC is epithelial-mesenchymal-transition (EMT). Integrin β₆ (ITGB6) is an inducer of EMT and has been associated with invasion of colon cancer cells. Here, we investigated the role of ITGB6 in colon cancer *in vivo*.

Methods: Azoxymethane (AOM)/dextran sodium sulphate (DSS) colon cancer model was induced in female ITGB6⁻/⁻ and C57BL/6J wild-type (WT) littermates, which were divided into a water (n = 6/9) and an AOM/DSS group (n = 11/14). Mice were treated 3 times for 7 days with 1% DSS and 14 days with water. At day 1 and 9 of each cycle, mice were treated intraperitoneally with AOM (10 mg/kg body weight) and killed 15 weeks after experimental start.

Results: AOM/DSS-treated ITGB6⁻/⁻ mice suffered from an aggravated DSS-induced colitis. By mouse endoscopy, we detected no tumours in AOM/DSS-treated ITGB6⁻/⁻ mice, whereas WT mice displayed up to 4 tumours per mouse. By histological analysis, AOM/DSS-treated WT mice displayed invasive infiltrating tumours up to the lamina muscularis mucosae of the intestinal epithelium.

Discussion/Conclusion: WT receiving AOM/DSS regularly developed colon tumours, whereas lack of ITGB6 completely protects mice from AOM/DSS-induced colon tumour formation. Moreover, we found an aggravation of colitis symptoms in ITGB6⁻/⁻ mice, whereas WT mice showed symptoms of a mild colitis. Our results suggest a potential role of ITGB6 during colon tumour development.
Loss of integrin β6 (ITGB6) results in aggravated acute and chronic DSS-induced colitis

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Introduction: Inflammatory bowel disease (IBD) represents a chronic inflammation of the intestine. During IBD, a continuous wound healing is ongoing in the intestinal epithelium, in which epithelial-mesenchymal-transition (EMT) might play a critical role. Integrin β6 (ITGB6) is exclusively expressed in epithelial cells and an inducer of EMT. Here, we investigated the role of ITGB6 during DSS-induced colitis in vivo.

Methods: Acute (AC) and chronic colitis (CC) was performed in female weight-matched ITGB6⁻/⁻ and C57BL/6J wild-type (WT) littermates. Mice were randomly assigned to a water (n = 5/8) and a DSS-treated group (n = 8/16). To induce an AC, mice were treated for 7 days with 1% dextran sodium sulphate (DSS) followed by 3 days of recovery. In the CC, mice were treated for 3 cycles, each for 7 days with 1% DSS followed by 14 days recovery with water.

Results: Upon DSS-treatment, ITGB6⁻/⁻ mice displayed signs of an aggravated colitis when compared to WT mice. In the AC, DSS-treated ITGB6⁻/⁻ mice showed pronounced shortening of the colon and an increased MEICS score. In the CC, these findings were similar to those obtained in the acute phase. Moreover, 56% of the DSS-treated ITGB6⁻/⁻ mice reached the termination criteria during the experiment.

Discussion/Conclusion: Lack of ITGB6 results in increased severity of DSS-induced acute and chronic colitis. This suggests that ITGB6 might play a critical role in the pathogenesis of intestinal inflammation, such as IBD.
Diagnosis and treatment management in digestive-cutaneous purpura in young patients

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The presence of vasculitic lesions at the level of skin and digestive mucosa, in young persons, is suggestive for Henoch-Schonlein purpura, involving, besides differential diagnosis, the establishment of proper treatment for immune correction.

**Aim:** To present therapy management in young patients with significant digestive symptomatology and purpuric skin lesions.

**Patients and Methods:** The study was conducted on eight women, aged 16–30 years old, who experienced severe gastrointestinal manifestations: abdominal pain, nausea, appetite loss and transit disorders. Simultaneously, they presented purpura at inferior limbs level and reported pharyngeal or sinus infections 2–3 weeks prior. Biologically, hemoglobin and platelets were normal, with a moderately elevated ESR, increased ASO and absence of Helicobacter pylori. Endoscopy revealed congestive petechial lesions at the level of gastric mucosa.

**Results:** Although digestive manifestations were the most severe, clinical and biological diagnosis was digestive-cutaneous purpura. Pathogenic treatment addressed primarily to inflammatory vascular lesions, both digestive and cutaneous. It required injectable corticosteroids and immunosuppression, in association with vascular-trophy medication, digestive mucosa protection and antisecretory drugs for complications. Symptomatology amelioration was achieved after 1–2 weeks. Eradication of infectious triggers is important in order to combat autoimmune events, to lower the recurrence and the necessary of corticosteroids.

**Conclusions:**
1. Digestive manifestations that associate cutaneous purpura, in young persons, are related to digestive mucosa vasculitic phenomenon, with autoimmune pathogenesis, most commonly post-streptococci.
2. Therapeutic management in digestive and skin purpura consisted of systemic corticosteroid therapy, which improved digestive symptoms, in association with vascular medication, antacids and protector drugs.
3. Antibiotic therapy was also associated, in the presence of an increased ASO titer and for the eradication of infectious outbreaks, as possible triggers.
4. Although digestive manifestations were severe, immune correction of vasculitic phenomena represented the main therapy and secondary, vascular-trophy therapy and digestive protector medication.
Mesalazine-induced thrombocytopenia and pericarditis in paediatric inflammatory bowel disease

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Introduction: We present two paediatric patients with inflammatory bowel disease (IBD) who developed serious adverse events to mesalazine in a district general hospital. Mesalazine has been used to treat IBD for several decades and was initially thought to be relatively free from serious side effects.

Methods: The information was collected from patient notes, electronic scans and blood results. A PubMed search was carried out.

Results: A 15-year-old girl with moderately-severe left hemicolitis was found to be profoundly thrombocytopenic after two days of treatment with oral mesalazine (Pentasa). Platelet count dropped from 212 to 20. Blood films showed neutrophil leukocytosis, no red cell fragments or blasts. She had no petechiae or mucosal bleeding. Mesalazine was immediately stopped and she received two platelet transfusions. Her platelet count recovered.

The second case is a 12-year-old girl treated with oral mesalazine (Salofalk®) for four months for ulcerative colitis. She presented with pericarditis four days after a dose increase. She was short of breath with chest pain, and had muffled heart sounds and a pericardial rub. An echocardiogram confirmed a global effusion with signs of haemodynamic compromise. Pericardial fluid analysis found pus cells, no bacterial growth and negative viral PCR. She recovered after cessation of mesalazine, pericardio-centesis and prednisolone.

Discussion/Conclusion: Serious adverse effects to mesalazine could be more common than previously thought. To our knowledge, this is the first published paediatric case study on mesalazine-induced thrombocytopenia. Pericarditis is known to be a rare side effect of mesalazine. We conclude that side effects of mesalazine and extraintestinal manifestations of IBD should always be considered in acutely unwell patients. Patients should have regular complete blood profiles monitored in short and long term treatment to detect haematological abnormality. Mesalazine should be promptly stopped if adverse reactions are suspected.
**MiR-155 plays a central role in Th17 cell development and in the pathogenesis of intestinal inflammation**

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**Introduction:** The dysregulation of our immune system, in particular the balance between pro- and anti-inflammatory signals by T-cells plays a central factor in inflammatory bowel diseases. Micro RNAs (miRNAs) are small regulatory molecules, playing an important role in many pathways. We demonstrate the importance of MiR-155 in the development of pro-inflammatory Th17 cells as well as its role in the establishment and maintenance of colitis.

**Methods:** Lymphocytes derived from MiR-155−/− and WT spleens were sorted for CD4+ CD25- T-cells and stimulated towards the Th17 lineage. The expression levels of miRNAs in mice receiving 2% DSS drinking water as well naïve and differentiated T-cells were investigated by qPCR. CD4+ CD25- T-Cells were adoptively transferred into RAG−/− mice, weight and inflammation was followed up for 5 weeks. Lamina propria cell populations were analysed by FACS, colon sections were analysed by IHC. Supernatants derived from organ cultures of lymph node and lamina propria cells were analysed by ELISA.

**Results:** Investigating the expression levels of miRNAs in DSS induced acute colitis and in naïve murine T-cells driven towards the Th17 lineage revealed a central function of miR-155. MiR-155 deficient T-cells show normal proliferation, however, are severely impaired in Th17 lineage commitment. We examined the function of miR-155 in a colitis model by adaptive T-cell transfer, uncovering a substantial role for miR-155 in the establishment of the inflammatory phenotype: RAG−/− mice that received miR-155 deficient T-cells developed reduced numbers of Th17 cells, reduced levels of Th17-associated cytokines and consecutively showed a delayed onset and overall diminished inflammation.

**Discussion/Conclusion:** MiR-155 is crucial for the development of the Th17 lineage and the subsequent establishment of the intestinal inflammation in a model of adoptive transfer colitis. Targeting miR-155 may prove to be an effective tool in controlling excessive immune responses, not limited to the gut.
**Viral modulation of extrinsic cell death pathways**

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**Introduction:** Recently it was shown that mice lacking caspase-8 in intestinal epithelial cells (IECs, Casp8ΔIEC) spontaneously developed inflammatory lesions in the terminal ileum and showed a high amount of Paneth cell death, called necroptosis, which is suggested to play an important role in the pathogenesis of Crohn’s disease. The caspase-8 activity is regulated by cellular FLIPs (cFLIPs). We could already show that mice lacking cFLIP in IECs die due to uncontrolled caspase-8 activity, leading to massive apoptotic epithelial cell death. Interestingly certain viruses express a viral FLIP (vFLIP) which shares structural similarities with cFLIP. It is believed that vFLIP is expressed to actively manipulate the caspase-8 activity to mediate necroptotic cell death.

**Methods:** We generated mice lacking cFLIP in IECs but expressing KSHV-vFLIP (cFLIPΔIECxvFLIPVillinCreERT2-tg) and compared them with mice, lacking cFLIP in IECs (cFLIPΔIEC) or mice which overexpress KSHV-vFLIP (vFLIPVillinCreERT2-tg) after tamoxifen injection as well as controls. Additionally we generated mice, which consequently express vFLIP in IECs (vFLIPVillinCre-tg). Mice were analysed histologically by immunohistochemistry. Furthermore, we analysed the gene expression pattern by qPCR as well as the protein expression by Western Blot.

**Results:** Surprisingly cFLIPΔIECxvFLIPVillinCreERT2-tg mice survived much longer (6–15 days) and showed less epithelial barrier destruction and cell death as compared to cFLIPΔIEC mice. Additionally vFLIPVillinCre-tg mice showed a similar phenotype to Casp8ΔIEC mice, including spontaneous development of inflammatory lesions and Paneth cell death.

**Discussion/Conclusion:** Our results indicate that KSHV-vFLIP is at least able to partially compensate for cFLIP, leading to a prolonged survival of cFLIPΔIECxvFLIPVillinCreERT2-tg mice compared to cFLIPΔIEC mice. Furthermore, vFLIPVillinCre-tg mice show a dramatic phenotype similar to Casp8ΔIEC mice, suggesting that the virus is able to manipulate the host cell death machinery, including caspase-8, by expressing vFLIP. These findings indicate a potential contribution of viruses to the development of Crohn’s disease.
ERAP1 gene polymorphisms in Turkish patients with inflammatory bowel disease and ankylosing spondylitis

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Background: Although genetic factors are known to play a crucial role in the pathogenesis of ankylosing spondylitis (AS), little is known about the molecular mechanisms that are responsible. In this context, the endoplasmic reticulum aminopeptidase 1 (ERAP1) gene has been suggested as the most important factor in genetic susceptibility in addition to HLA-B27.

The aim of this study is to investigate the role of ERAP1 in the pathogenesis of AS and inflammatory bowel disease, and its relationship with clinical findings.

Methods: Our study included 273 consecutive AS patients who fulfilled the modified New York classification criteria, 50 patients diagnosed with Crohn’s disease, 39 patients diagnosed with ulcerative colitis based on endoscopic, radiographic and pathologic findings, 60 patients diagnosed with enteropathic arthritis and 230 blood donors as healthy control subjects.

DNA was automatically isolated from the participants’ blood samples using the QIAGEN system. We investigated the presence of ERAP1 gene single nucleotide polymorphisms (SNPs) (rs26653) using the method of competitive allele-specific PCR. We also determined the subgroups of HLA-B27 using PCR sequence-specific primers (PCR-SSP). All patients and healthy controls were subject to Hardy-Weinberg equilibrium (HWE) testing. The differences between genotype and allele frequencies were compared using Pearson’s chi-square test. The odds ratio (OR) and 95% confidence intervals (CI) were calculated.

Results: The mean age of the patients was 38.3 ± 11.8 years: 39.8 ± 12.9 years for Crohn’s disease patients, 38.9 ± 12.5 years for ulcerative colitis patients, 38.3 ± 11.8 years for enteropathic arthritis patients and 38.0 ± 8.9 years for the controls. The rate of HLA-B27 positivity was 74.3% in the AS patient group, 18.9% in the Crohn’s group, 21.2% in the UC group, 33% in the enteropathic arthritis group and 4.7% in the control group. We detected rs26653 SNP C/C homozygotes in 35 AS patients (12.8%) and 8 controls (3.5%), in 11 Crohn’s disease patients (22%) and 8 controls (3.5%), and in 7 UC patients (18%) and 8 controls (3.5%). The frequency distribution of the rs26653 SNP C/C homozygous genotype between the AS, Crohn’s disease and ulcerative colitis groups was found to be statistically significant (p = 0.015). (OR 4.08, 95% CI, 1.85–8.98, p = 0.0005). When compared to those of the control group, the genomic distribution and rare homozygote frequency in enteropathic arthritis patients were not found to be statistically significant. The same applied to other SNPs.
Conclusions: In our study, rs26653 SNPs, which have previously been suggested as genetic susceptibility factors in AS, were found to be associated with the risk of genetic predisposition in our AS group. We were able to show the effect of ERAP1 polymorphism on the pathogenesis of Crohn's disease and ulcerative colitis, which had not been found in previous studies. In relation to this, larger-scaled studies with inflammatory bowel disease patients in particular are needed. Specifically, rs26653 polymorphism may play a role in the development of spondyloarthritis in Turkish populations.
Treatment of dysbiosis in uncomplicated diverticular disease of the colon

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Introduction: Available data show the efficacy of poorly absorbed antibiotics and dietary fiber in patients with uncomplicated diverticular disease. Our aim was to evaluate the long-term efficacy of rifaximin and dietary fibers in reducing symptoms and to prevent recurrent attacks and complications such as diverticulitis.

Methods: 282 patients (161 males, 121 females, age 65.4 ± 7.4 years) from two gastroenterological units were randomly enrolled in two treatment schedules: group 1 (172 pts) rifaximin 400 mg BID; group 2 (110 pts) dietary fiber supplementation (Colon Help 20 g/day). Treatments were administered 10 days every month for 9 months. Inclusion criteria were: endoscopic and/or radiologic evidence of diverticular disease of the left colon and the presence of symptoms attributable to diverticular disease without signs of diverticulitis.

Results: Clinical (Global Symptomatic Score, GSS), endoscopic and imagistic evaluations were performed at admission and 3 month intervals. The efficacy in reducing tenesmus, bloating, diarrhea, well-being and bleeding was greater in group 1 (p < 0.0001; p = 0.01; p = 0.01; p = 0.01 and p = 0.04, respectively after 9 months). GSS declined in both groups, but a greater reduction was evident in the rifaximin group (intention-to-treat analysis 3.31 ± 2.68 vs. 5.86 ± 4.55, p < 0.001; per-protocol analysis: 3.50 ± 2.56 vs. 6.32 ± 4.21, p < 0.001). The patients treated with rifaximin showed a more marked reduction in symptom frequency. Complications occurred in 5 patients of group 1 (3 cases of rectal bleeding and 2 of diverticulitis) and in 9 patients of group 2 (3 cases of intestinal infections, 2 of rectal bleeding and 4 of diverticulitis) (p = 0.031). Side effects occurred in 7 patients of the rifaximin group and 5 patients of the fiber group (p = n.s.).

Discussion/Conclusion: Cyclic administration of rifaximin and dietary fiber is effective for symptomatic relief of uncomplicated diverticular disease of the colon. Some symptoms and complications showed greater improvement with rifaximin, which is safe and well-tolerated by patients.
Extra-colonic cancer risk in collagenous colitis

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Introduction: Collagenous colitis (CC) is a clinic-pathological syndrome of chronic/watery diarrhoea and its worldwide incidence is increasing [1]. Most epidemiologic and interventional studies are concerned with the potential of spontaneous remission or treatment/post-therapy relapse, respectively [2]. Nevertheless, data on the incidence of extra-colonic malignancy in CC is scarce [3]. The aim of the present study was to determine the occurrence of extra-colonic malignancies in patients with CC.

Methods: A retrospective, two-centre study; data on extra-colonic cancer in patients with CC were collected for a 14-year period (2000–2013). Person years at risk was calculated according to age-specific categories up to 85 years [4]. The standard error (Se) was calculated using the Poisson approximation. Confidence interval (CI) of the age-standardised rate (ASR) was compared to public data, available from http://www.ncin.org.uk/cancer_information_tools/eatlas/guide [5]. Relative risk (RR) for ASR was calculated and compared to ASR in Lothian [4]. The standardised cancer incidence rates (IR) were also compared to the ones of Lothian Scotland under the assumption that populations at the same latitude share the same IR.

Results: In total, 738 patients (394 Edinburgh/344 Malmö) with CC were included. 71 (50F/21M: group A) developed some form of extra-colonic malignancy following the diagnosis of CC (remainder 667: group B). The average age of group A was 70.6 ± 10.9 years, while that of group B was 66.0 ± 13.5 years. The average follow-up (F/U) duration of group A was 3 ± 2.9 years, while the average duration of the cases until the occurrence of cancer was 5 ± 3.8 years.

The RR for all cancers (36.79; CI: 34.5;39.25), lung (3.88, CI: 1.62;9.31), bladder (9.23; CI: 1.14;75.03) and skin cancer (14.96; CI: 2.57;87.08) as well as the ASR in patients with CC is higher compared to the general population (Lothian data). Lung cancer may be explained by the association between CC and smoking, while the observations in bladder and skin cancers warrant further studies.

Discussion/Conclusion: The RR of all extra-colonic cancers, lung, bladder and skin cancer is higher in patients with CC.
References:

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Clinical-biological particularities of non-alcoholic fatty liver disease in Romanian patients

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Introduction: I present a prospective observational investigation of 125 Romanian fatty liver patients.

Methods: I watched the degree of liver steatosis and concomitant appearance of predisposing co-morbidities trying to point out correlations between clinical aspects and laboratory examinations.

Results: The most common symptoms were asthenia and fatigue. The most common co-morbidities were cardiovascular diseases and diabetes mellitus. Analyses of lifestyle reveal a significant percentage of patients that recognize a sedentary lifestyle (79.2%), low or medium fruit and vegetables intake, imbalanced nutrition. Many patients present at least one components of metabolic syndrome: dyslipidemia 72%, obesity 67%, hypertension 60%, diabetes 40.8%. I found significant linear correlations between fasting blood glucose-triglycerides (r = 0.25) respectively BMI (r = 0.23), a close positive correlation between ALT/GGT (r = 0.33) and also fasting glucose/age (r = 0.25). I observed significant correlations between age and glucose, triglycerides, BMI, ALT. Averaged values of EPO, CRP, IL-6, TNF and IL-8 were higher than normal, signifying the participation of these cytokines in the inflammatory process, pathogenesis of inflammation, fibrosis. I found a close linear correlation between levels of TNF-IL-6, IL-6-PCR, TNF-CRP and association between CRP-GGT, GGT-IL-6. There was a significant linear correlation between inflammation markers and fibrosis Forns index (IL-6-Forns: r = 0.47, TNF-Forns: r = 0.32, EPO-Forns: r = 0.25). Framingham cardiovascular risk score and SCORE increased with age (Spearman coefficient: r = 0.64, respectively 0.47).

Discussion/Conclusion: The results confirm data that non-alcoholic fatty liver is a common adult population disease accompanied by multiple co-morbidities mainly metabolic syndrome. It is justified an action of aggressive prevention, correction and treatment of obesity and associated factors by promoting physical exercise (the cheapest and effective treatment), and a style of healthy eating, in order to prevent cardio-metabolic morbidities and advancing liver fibrosis.
Infliximab or adalimumab for Crohn's disease

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Introduction: In the latest years the biological treatment with antibodies against tumor necrosis factor-α is widely used for patients with Crohn’s disease (CD). The aim of this study is to compare the efficacity of the two of the most commonly used biological agents: infliximab and adalimumab.

Methods: We conducted a retrospective study which included 66 patients with CD hospitalized between 1 January 2011 and 31 December 2014 in Institute of Gastroenterology and Hepatology, Iasi. All the patients were new users of infliximab (n = 25) or adalimumab (n = 41). We measure the disease persistence on therapy at week 26, relapse on therapy, hospitalization and the need for surgery.

Results: 68% of patients receiving infliximab remained on drug on week 26, compared with 66% of those receiving adalimumab (odds ratio, 0.98; 95% CI, 0.71–1.17). Two patients treated with infliximab have to switch therapy on adalimumab and three patients with adalimumab have to switch therapy for adalimumab. Only one patient treated with adalimumab underwent surgery. Rates of hospitalization did not differ between groups (odds ratio, 0.85; 95% CI, 0.78–1.01).

Discussion/Conclusion: There are no significant differences between the effectiveness of infliximab and adalimumab for CD.
Prevalence of celiac disease in patients with cystic hydatid disease: May they have been related to same environmental conditions?

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Objective: Celiac disease (CD) is a small intestinal malabsorption syndrome and is caused by hypersensitivity to gluten in subjects who carry HLA haplotypes HLA DQ2 and DQ8. This hypersensitivity reactions result in chronic inflammatory reaction in the small intestine and lead to a broad spectrum of symptoms and findings including chronic diarrhea, failure to thrive, anemia, arthritis, osteopenia, elevated liver enzymes and lower albumin levels. This is underestimated by the fact that it remains under recognized in almost 90% of patients. Cystic hydatid disease (CHD) can be localized in every organ and CHD is an important public health issue in some countries including Turkey. The disease localized in liver and lungs in most the cases and has been associated with a variety of hematologic and biochemical manifestations. It has been well known that both CD and CHD are prevalent in rural areas of the Mediterranean basin. Other hand early identification of CD is essential to be able to achieve better outcomes. We therefore tried to show the connection between CD and CDH.

Material and Methods: We prospectively analyzed data from 211 CHD patients (mean age 36.2 ± 19.4 years; 87 male). 62 of them had extrahepatic involvement of CHD. In addition, patients’ hydatid cysts classified as their radiologic features (49 had type 1; 42 had type 2; 40 had type 3; 18 had type 4 and 9 had type 5). All patients tested positive for CHD by ELISA. Sera from study population were also analyzed for IgA, IgG, with ELISA using human recombinant tTG (AESKULİSA, Aesku. Diagnostic, Germany). Comparator group (100 subjects; 50 male; mean age 38.5 ± 18.6 years) was selected from subjects who admitted to our internal medicine clinic for other reasons. Patients with serum IgA deficiency and those with prior diagnosis of CD were excluded from the study. Chi-square test was performed in determining the relationship between categorical variables and groups. Significance limit was taken as p < 0.05 and duplex. Analyses were performed using SPSS 21 software.

Results: There were 12 (5.7%) seropositivity of tTG IgA among patients with CHD. In the control group, the rate of tTG IgG seropositivity was only 2 (2%) and was lower than those with CHD (p < 0.05). In patients with CHD, mean WBC level was higher in patients with tTG IgA seropositivity compared to those without seropositive tTG IgA (11,333/mm³ vs. 8,401/mm³; p = 0.05). On the other hand, lower age was independently associated with TTG IgA seropositivity in CDH group (36.91 ± 9.4 versus 25.8 ± 15.4 years; p = 0.043).
**Conclusion:** Higher rate of seropositivity of tTG IgA antibodies among patients with CHD may reflect a unique phenomenon that requires further investigation to determine underlying causative factors. We also concluded that younger CHD patients with higher WBC levels should be tested for possible CD. This study furthers the understanding of CD risk in CHD. If confirmed by future studies, these data due to assist in developing optimal strategies for detecting of CD in patients with CHD.
Intestinal anti-inflammatory effects of total alkaloids of Fumaria capreolata in the DNBS model of mice colitis

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Introduction: Total alkaloids fraction extracted from the aerial parts of Fumaria capreolata (AFC), an herbaceous herbal plant that grows in Europe, has shown to exert immunomodulatory properties, without exerting adverse effects in vivo. The aim of this study was to evaluate the effects of AFC in the DNBS model of colitis.

Methods: Acute intestinal inflammation was induced by intrarectal administration of DNBS (4 mg) in 50% ethanol to CD1 mice. Once colitis was induced, mice were treated with different doses of AFC (100, 50 and 25 mg/kg); a colitic control and non-colitic groups were included for reference. After 5 days, all groups were sacrificed and the colonic specimens were evaluated by determining the expression of proinflammatory markers by qRT-PCR.

Results: The administration of AFC showed intestinal anti-inflammatory effects as evidenced by a reduction in body weight loss and colon weight/length ratio in comparison with non-treated colitic group. Biochemically, this beneficial effect was evidenced by a significant inhibition of the release and expression of IL-6 and TNF-α. It also suppressed the transcription of other pro-inflammatory factors such as IL-1β, iNOS, IL-12 and IL-17. Besides, the beneficial effect of AFC was associated with the normalization of the expression of MUC-2 and ZO-1, involved in epithelial integrity.

Discussion/Conclusion: AFC showed intestinal anti-inflammatory effect in the DNBS model of mouse colitis through the amelioration of the altered immune response and improvement of the epithelial barrier function.
The antidepressant agomelatine reduces intestinal inflammation in DNBS experimental colitis in mice

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Introduction: Intestinal inflammatory conditions frequently interact with depression and anxiety, having mood and stress a great impact in digestive disorders. Agomelatine is a novel well-tolerated antidepressant that combines melatonin agonistic and 5-HT2 antagonistic properties, both of great interest for the treatment of intestinal inflammation and the stress associated with this process. Therefore, we aimed to evaluate the effect of agomelatine in the DNBS model of colitis.

Methods: Acute intestinal inflammation was induced by intrarectal administration of DNBS (4 mg) in 50% ethanol to CD1 mice anesthetized with isoflurane. After 6 days of treatment with oral agomelatine (50, 25 and 12.5 mg/kg), all groups were sacrificed and the colonic specimens were evaluated by determining the expression of proinflammatory markers and micro-RNAs by qRT-PCR.

Results: The administration of agomelatine showed intestine anti-inflammatory effects as evidenced by a reduction in weight loss and mortality in the colitic groups treated with the doses of 50 and 25 mg/kg. Biochemically, this beneficial effect was evidenced by reduced expression of different proinflammatory markers, including cytokines and chemokines, metalloproteinases and barrier function and leukocyte adhesion molecules; additionally, some of the microRNA evaluated were modified, achieving a significant reduction in miR-9 and miR-223.

Discussion/Conclusion: Agomelatine showed a direct intestinal anti-inflammatory effect, increasing the survival to an acute intestinal inflammation and affecting both the immune response and epithelial barrier function. Modifications achieved in some of the microRNAs could be involved in the mechanism of agomelatine directly reducing the inflammatory response.
Pentoxifylline and prednisone versus prednisolone for severe alcoholic hepatitis

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Introduction: Alcoholic hepatitis is a clinical syndrome characterized by jaundice and liver impairment that occur in patients with a history of heavy and prolonged alcohol use. Prednisolone and pentoxifylline are both recommended for the treatment of alcoholic hepatitis.

Aim: To compare the efficacy of the association between prednisolone and pentoxifylline and prednisolone alone in the treatment of alcoholic hepatitis.

Methods: During January 2011 and December 2014, we conducted a prospective study that included 72 patients with severe alcoholic hepatitis. The follow-up period for each patient was one month. The patients were divided into two groups: group I (n = 36) received pentoxifylline (400 mg thrice/day) with prednisolone (40 mg/day) and group II (n = 36) prednisolone (40 mg/day) alone for 28 days. Patients with active infection, bleeding, renal failure or pancreatitis were excluded.

Results: The baseline characteristics of the two groups were related. The evolution was assessed by serum level of liver transaminases (LTS), bilirubin and prothrombin time (PT). Upon admission, the serum level of the biological markers was similar, with no significant differences between groups. After one week, the serum levels of bilirubin were considerably lower in both groups, although for the patients from group I, this improvement was superior (p = 0.025). PT amelioration was noted only in group I, without significant differences between the two groups (p = 0.025), while LTS improved in both groups. After 28 days, significant improvement was noticed in both groups, as regards bilirubin levels (group I, p = 0.001; group II, p = 0.003) and PT (group I, p = 0.001; group II, p = 0.004); however, for the patients in group I, the improvement was significantly better compared to the patients in group II (p = 0.007). As regards the serum levels of LTS, no statistical difference between the groups was noticed following the 28 days evaluation.

Discussion/Conclusion: Our study suggests that 4-week treatment with pentoxifylline and prednisolone is superior compared to prednisolone alone in patients with severe alcoholic hepatitis. However, other studies have shown that the association of corticosteroids and pentoxifylline has no additional survival advantage compared to corticosteroids alone. Further research is needed to provide more data for the improvement of the outcome in patients with alcoholic hepatitis.
Medical history of eradicated Helicobacter pylori infection as an individual risk factor for gastric cancer

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Introduction: The aim was to assess the relationship between precancerous changes (PC) and a medical history of eradicated Helicobacter pylori (HP) infection and determine the effect of this association on the development of gastric cancer (GC).

Methods: Our multi-annual retrospective study included 125 patients with pre-existing PC. The A group consisted of 77 patients with a medical history of HP infection eradicated three years ago (HP absence monitored over the last three years), and the B group contained 48 patients that had never been infected with HP. The medical history and duration of HP eradication were also quantified. We monitored the development of PC and compared the cancer risk in these groups.

Results: The incidence of PC was: atrophic gastritis (66 cases), gastric ulcer (18 cases), gastrectomy (23 cases), gastric polyps (13 cases) and Ménétrier gastritis (5 cases). The A group contained all of the Ménétrier gastritis cases, atrophic gastritis (41 cases), gastric ulcer (12 cases), gastrectomy (9 cases) and gastric polyps (10 cases). 29 patients (37.66%) developed GC in the A group and 8 patients (16.66%) in the B group. The majority of Ménétrier gastritis patients (4 cases) developed GC. In the A group, endoscopic forms of early-stage GC were: type I (polypoid) in 8 cases, type II (superficial) in 4 cases and type III (ulcerated) in 5 cases. With regards to advanced GC, we found Borrmann type I in 4 cases, Borrmann type II in 7 cases and Borrmann type IV in just one case. Patients in group B also developed advanced GC: Borrmann type II (4 cases) and Borrmann type III (3 cases). Early-stage GC was found in just one case.

Compared with other PC, atrophic gastritis was more frequently associated with a medical history of HP infection (p = 0.01). The risk of developing GC was not linked to the duration of HP eradication (r = 0.103, p > 0.05) or the number of successful treatments.

Discussion/Conclusion: Precancerous changes in connection with a medical history of eradicated HP infection are associated with an increased risk of developing gastric cancer in comparison to patients that have never suffered from the infection. Atrophic gastritis was more frequently associated with a medical history of HP infection.
Sequential therapy for Helicobacter pylori eradication as a first-line treatment for patients with type 2 diabetes

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Introduction: The aim was to assess the efficacy and safety of sequential therapy for Helicobacter pylori (HP) eradication as a first-line treatment.

Methods: This multi-annual retrospective study included 88 patients suffering from HP infection. The A group consisted of 39 patients with type 2 diabetes mellitus (disease history was longer than 3 years) and the B group contained 49 non-diabetic patients. The first-line therapy for HP eradication was: conventional triple therapy (10 days of pantoprazole, 2 x 20 mg/day, amoxicillin 2 x 1000 mg/day and clarithromycin 2 x 500 mg/day) in 57 cases and sequential therapy (5 days of pantoprazole and amoxicillin followed by 5 days of pantoprazole, clarithromycin and metronidazole) in 31 cases. The medical history and duration of HP eradication (eradication rate, drug compliance, and side effects) were quantified and compared. We monitored the development of glycosylated hemoglobin (HbA1c) values and BMI during the course of treatment and one year after HP eradication.

Results: Sequential therapy for HP eradication was trialed in both groups: 18 cases (46.16%) in patients with type 2 diabetes mellitus and 25 cases (51.02%) in non-diabetic patients. The eradication rate was lower in patients with type 2 diabetes mellitus (76.93%, 30 cases) compared with non-diabetic patients (91.84%, 45 cases). In patients with type 2 diabetes, sequential therapy proved to be more effective than conventional triple therapy: The eradication rate was 83.34% (15 cases) after sequential therapy and 71.43% after standard therapy. In non-diabetic patients, the HP eradication rate was similar in both treatments: 91.6% for standard therapy versus 92.1% for sequential therapy. We did not observe significant variations in the mean value of glycosylated hemoglobin (HbA1c) during or after HP eradication therapy. We found a significant increase in the mean value of BMI in diabetic patients 6 months (22.8 ± 3.2 kg/m² vs. 21.3 ± 2.9 kg/m² at baseline) and 12 months (23.9 ± 3.8 kg/m²) after HP eradication. The BMI increase was similar in both treatment options. In the B group, the variation in the BMI average was not significant. The incidence of side effects during treatment was reduced in both groups and consisted of: abdominal pain (5 cases), nausea and/or vomiting (6 cases) and diarrhea (3 cases).

Discussion/Conclusion: Sequential therapy for HP eradication proved to be more effective and safe in patients with type 2 diabetes mellitus in comparison to standard therapy. HP eradication was associated with an increased BMI in diabetic patients.
Molecular profiling with determination of KRAS TP53 and KIT mutations with further clinical implications for adenocarcinomas of ventricular cardia of a mother and a daughter

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Introduction: We aimed at investigation of gene mutations in gastric adenocarcinomas of ventricular cardia in 57-year-old woman and her 39-year-old daughter to determine eventual predictive factors for possible target therapy.

Methods: Both of neoplasms were surgically removed by Ivor-Lewis esophagogastrectomy. The microscopic slides were routinely stained with H&E. Immunohistochemical evaluations included chromogranin A, AFP, Vimentin and CK MNF 116. Additionally we examined status of following genes ABL1, EZH2, JAK3, PTEN, AKT1, FBXW7, IDH2, PTPN11, ALK, FGFR1, KDR, RB1, APC, FGFR2, KIT, RET, ATM, FGFR3, KRAS, SMAD4, BRAF, FLT3, MET, SMARCB1, CDH1, GNA11, MLH1, SMO, CDKN2A, GNAS, MPL, SRC, CSF1R, GNAQ, NOTCH1, STK11, CTNNB1, HNF1A, NPM1, TP53, EGFR, HRAS, NRAS, VHL, ERBB2, IDH1, PDGFRA, ERBB4, JAK2, PIK3CA by using NGS (IonTorrent – IonAmpliSeq Cancer Panel v2 – LifeTechnology, USA).

Results: The tumors were mucocellular carcinoma of diffuse Lauren type (signet ring cell carcinoma) pT3N1 of the mother and poorly differentiated adenocarcinoma G3 pT4a N3b of ventricular cardia of the daughter respectively. The mother carried mutation TP53 (7579358 C>A p.R110L frequency 46.1%) and KRAS mutation of codon G12V (25398284 C>A, p.G12V frequency 58.7%) in tissues of primary tumor. Similarly TP53 (7579358 C>A p.R110L frequency 56.2%) and KRAS (25398284 C.A p.G12V frequency 53.2%) mutations were detected in nodal metastasis of primary maternal cancer. The daughter presented TP53 (7579358 C>A p.R110L frequency 53.2%) and KRAS mutations (25398284 C.Ap.G12V frequency 56.2%). However, we detected also p.G565R c.1693G>A (frequency 21%), p.Q575H (c.1718G>A, frequency 20%) in KIT gene and PTEN p.V249M in the daughter’s tumor.

Discussion/Conclusion: It is very crucial to screen formalin-fixed, paraffin-embedded (FFPE) material for presence of any gene mutations of predictive and prognostic significance to determine at least KRAS, TP53 and KIT gene status, especially if cancers occur in close family relatives as in our cases.
Metabolic syndrome and probiotics

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Introduction: Metabolic syndrome is defined by central obesity, raised fasting plasma glucose, high triglycerides, low high-density lipoprotein and arterial hypertension, with addition of low-grade inflammation processes in the visceral fatty tissue. All components contribute to the development of cardiovascular diseases. It is known that probiotic bacteria have influence on health improvement, and can exert positive effects on diseases as the metabolic syndrome.

Aim of the study: To evaluate potential positive effects of probiotic bacteria Lactobacillus plantarum PCS 20, PCS 26 and Lactobacillus rhamnosus GG.

Materials and Methods: Probiotic strains were evaluated using non-carcinogenic human small intestinal epithelial cells HIEC, H4-1 and HUIEC, human monocytes/macrophages TLT and human visceral preadipocytes VPA. With H4-1 and HUIEC cells, all three probiotic strains were tested for potential cytotoxicity and the ability to adhere to intestinal epithelia. Furthermore, the strains were tested for their ability to remove cholesterol from the media and to express bile salt hydrolase activity. Subsequently, HIEC and HUIEC cells were used to evaluate the ability of probiotic strains to modulate mRNA expression of cholesterol homeostasis genes NR1H3, NR1H2, NPC1L1, ABCG5, ABCG8 and LPL. In addition, 3-dimensional functional cell models were constructed with HUIEC cells on the apical side and TLT, VPA or mixed TLT/VPA cells in the basolateral compartment in order to evaluate the secretion of TNF-α, IL-4, IL-12 and IL-13 in the presence of probiotic strains.

Results. All three probiotic strains did not exert any cytotoxic effects on the cells and were able to adhere to intestinal epithelia. Probiotic strains have also shown the ability to remove cholesterol from the media, but bile salt hydrolase activity was determined only by PCS 20 and PCS 26 strains. Both Lactobacillus plantarum PCS 26 and PCS 20 strains have shown the potential to promote biliary cholesterol efflux or inhibit intestinal cholesterol absorption through up-regulation of liver X receptors (NR1H3 and NR1H2) and subsequent regulation of their target genes NPC1L1, ABCG5, ABCG8 and LPL. Additionally, Lactobacillus plantarum PCS 26 was able to promote secretion of IL-13 and TNF-α in the 3D functional cell model constructed from intestinal epithelial cells and monocytes/macrophages.

Conclusion. We found that the probiotic strains exert positive effects, which could help to relieve the particular components of the metabolic syndrome as they can act as liver X receptor agonists and thus improve the lipid profiles or may help to promote IL-13 secretion, which can positively affect atherosclerotic lesions and inhibit the glucose production in the liver.
Influence of the intestinal microbiota on expression of cell death regulators

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Introduction: Intestinal epithelial necroptosis is a newly described hallmark of intestinal inflammation and has been discussed as a possible pathogenic mechanism driving Crohn’s disease in humans. We specifically aim to investigate the influence of the microbial flora on the regulating of necroptosis.

Methods: We have evaluated the expression of various cell death executor molecules in the terminal ileum of germfree animals and mice which has been reconstituted with SPF flora.

Results: Interestingly we could observe that MLKL, a key mediator of necroptosis, was significantly upregulated during colonization with SPF flora. We further identified that interferons (IFNs), cytokines that were also transcriptionally activated during colonization mediate, MLKL upregulation. We further demonstrate that both type-I and type-III IFNs can trigger MLKL upregulation. Moreover, stimulation of organoids with IFNs causes massive cell death with necrotic morphology, suggesting a non-apoptotic form of cell death. This was supported by the fact that mice deficient for caspase-8 in intestinal epithelial cells (Caspase-8¹IEC mice) showed excessive cell death associated with high mortality in response to IFN. Disruption of barrier function required Rip3, since Rip3⁻⁻Caspase-8¹IEC animals were protected from IFN induced epithelial cell death, indicating that this form of cell death is due to Rip3-mediated necroptosis. In a translational approach, we identified a strong induction of MLKL and IL28 gene transcription in intestinal epithelial cells of CD patients, suggesting a potential contribution of these factors to the pathogenesis of CD.

Discussion/Conclusion: Our data demonstrated that the intestinal microbiota can promote necroptosis by upregulating the central necroptosis mediator MLKL. Moreover, we showed for the first time that MLKL is strongly upregulated in CD patients, supporting the hypothesis that necroptosis could be involved in the disease pathogenesis. We anticipate our finding to be a starting point to elucidate novel disease mechanism and will potentially help to identify novel therapeutic options for IBD patients.
**Decreased fibrogenesis upon pirfenidone in a newly developed mouse model of intestinal fibrosis**

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**Introduction:** Fibrosis as a common problem in patients with Crohn’s disease (CD) is a result of an imbalance towards excessive tissue repair. At present there is no specific treatment option for CD patients with recurrent intestinal fibrosis. Pirfenidone is a small molecule approved for the treatment of idiopathic pulmonary fibrosis with both anti-fibrotic and anti-inflammatory effects. We subsequently investigated the impact of pirfenidone treatment upon development of fibrosis in a new mouse model of intestinal fibrosis.

**Methods:** Small bowel resections from donor-mice were transplanted subcutaneously into the neck of recipients. Animals received either pirfenidone (100 mg/kg administered three times a day orally) or vehicle. Intestinal grafts were examined for collagen layer thickness, expression of mediators of fibrosis and cytokines.

**Results:** Upon pirfenidone a significantly decreased collagen layer thickness was revealed as compared to vehicle (9.7 ± 1.0 vs. 13.5 ± 1.5 µm, respectively, **p < 0.001). Important mediators of fibrosis such as TGF-β and MMP-9 were significantly decreased upon administration of pirfenidone as confirmed by qPCR (0.42 ± 0.13 vs. 1.00 ± 0.21 and 0.46 ± 0.24 vs. 1.00 ± 0.62 mRNA expression level relative to GAPDH, respectively, *p < 0.05). Significantly decreased TGF-β upon administration of pirfenidone was confirmed by Western blot.

**Discussion/Conclusion:** In our new established mouse model intestinal fibrosis can be reliably induced and is developed within 7 days. Pirfenidone partially prevented development of fibrosis making it a potential treatment option against CD associated fibrosis. Further studies will be necessary to develop this option.
The role of epithelial caspase-8 during infection with *Salmonella typhimurium*

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**Introduction:** Deficiency of caspase-8, a central apoptotic regulator, in intestinal epithelial cells (IECs) of mice leads to spontaneous ileitis and increased sensitivity towards DSS-induced colitis. We now investigated the role of epithelial caspase-8 in infectious colitis.

**Methods:** After pre-treatment with streptomycin, we infected Caspase-8$^{ΔIEC}$ mice and control animals with *Salmonella typhimurium*. We followed survival and weight loss over time. Gene expression patterns and histology of tissue sections were analyzed by quantitative PCR and immunohistochemistry respectively.

**Results:** In contrast to wild type mice, Caspase-8$^{ΔIEC}$ mice showed a high lethality after infection. Excessive cell death and the following barrier breakdown enable the pathogens and the commensal gut microbiota to invade into subepithelial areas, resulting in a systemic infection. This might be caused by the absence of Paneth cells and a reduced number of goblet cells in the intestine, which both have a crucial role in the antimicrobial defense and therefore maintaining the mucosal barrier in the gut. Due to this failure in antimicrobial defense, Caspase-8$^{ΔIEC}$ mice harbor a significantly higher bacterial load, while wild type mice are able to clear the infection. Although RNA data did show a massively increased expression of pro-inflammatory markers, an altered expression of antimicrobial peptides in the colon of control versus Caspase-8$^{ΔIEC}$ mice challenged with *S. typhimurium* could not be shown. This suggests that probably an altered intestinal microflora, which is present in Caspase-8$^{ΔIEC}$ mice, might enable *S. typhimurium* to replicate more extensively.

**Discussion/Conclusion:** Our data demonstrate a crucial role for caspase-8 in controlling intestinal homeostasis and barrier maintenance in response to infectious colitis.
IgG4-related autoimmune pancreatitis, a mimicker of pancreatic cancer

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Introduction: IgG4-related autoimmune pancreatitis (IgG4-AIP) is a rare form of chronic pancreatitis, which could mimic pancreatic cancer. Clinical distinction is often difficult as both diseases affect patients at the age group 50+, have the same occurrence of jaundice, weight loss, mild abdominal discomfort or pancreatic mass, and their diagnostic criteria could to some degree overlap. In histology finding, IgG4-AP is characterised by dense infiltration of IgG4-positive plasma cells and extensive fibrosis. In IgG4-AP is typically elevated level of IgG4 in serum (> 140 mg/dl), and IgG4-AIP is responsive to corticosteroid therapy.

Case report: 68-year-old man presented with a history of weight loss and painless jaundice. Laboratory revealed typical biochemical markers of obstructive jaundice; levels of C-reactive protein, amylase and tumor marker CA 19-9 were normal. Abdominal CT (Figure 1) showed mass in the head of the pancreas. In ERCP, biliary stent was unable to place due to rigidity of papilla of Vater. Surgical exploration demonstrated rigid mass of pancreatic head and rigidity of body and tail. Gross pathological finding showed a firm yellowish mass mainly in the pancreatic head (Figure 2). Microscopic evaluation revealed typical signs of IgG4-AP (Figures 3 and 4). Fibrosis and scaring involved also distal part of ductus choledochus causing its obstruction and creating the impossibility to place stent by ERCP. The serum IgG4 level was 352 mg/dl.

Conclusion: In patients with pancreatic masses one should bear in mind the possibility of other underlying disorder, namely an autoimmune pancreatitis except a still more probable pancreatic cancer. Accurate diagnosis can avoid major pancreato-biliary surgery. In ERCP, a rigidity of papilla of Vater belongs to signs which should rise a suspicion on IgG4-AIP.
Reduced volume regimen in colonoscopy using PEG-3350 (Endofalk®): Results of a randomised prospective study

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Moscow University Hospital No. 31, Moscow, Russia

Introduction: The usage of a high-volume dose of PEG is sometimes limited by the patient’s imperception that leads to poor colon preparation.

Aim and Methods: To evaluate the tolerability and effectiveness of the 2 l PEG-3350 (Endofalk®) regimen in combination with bisacodyl and sennosides in preparation to colonoscopy. From VIII.2014 to IV.2015 we have examined 72 pts. (m-25, f-47, mean age 50.9 ± 15.9 years, range 20–77) who were randomly assigned to receive either bisacodyl 15 mg (Reg. 1) or sennosides 27 mg (Reg. 2) in the evening followed by 2 l PEG-3350 in the morning before colonoscopy. The important item was a compliance with a low-fiber diet 3 days and liquids before colonoscopy. The tolerability assessed by the enquirer. The cleansing efficacy was graded using the Boston Bowel Preparation Scale (BBPS) (≥ 6 scores were considered as “successful preparation”).

Results: According to the results of enquirer the tolerability of Reg. 1 was better compared to Reg. 2 with differ significantly (p < 0.05).

<table>
<thead>
<tr>
<th>Tolerability</th>
<th>Reg. 1 (n = 35)</th>
<th>Reg. 2 (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- good</td>
<td>16 (45.7%)</td>
<td>12 (32.4%)</td>
</tr>
<tr>
<td>- satisfactory</td>
<td>19 (54.3%)</td>
<td>23 (62.2%)</td>
</tr>
<tr>
<td>- bad</td>
<td>–</td>
<td>2 (5.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Reg. 1 (n = 35)</th>
<th>Reg. 2 (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- dyspepsia syndrome</td>
<td>10 (28.6%)</td>
<td>13 (35.1%)</td>
</tr>
<tr>
<td>- nausea/vomiting</td>
<td>6 (17.1%)</td>
<td>10 (27.0%)</td>
</tr>
<tr>
<td>- abdominal discomfort</td>
<td>6 (17.1%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>- abdominal distension</td>
<td>3 (8.6%)</td>
<td>2 (5.4%)</td>
</tr>
</tbody>
</table>

| No complaints      | 10 (28.6%)     | 9 (24.3%)     |

In spite of reduced preparation regimen only 64 (88.8%) pts. followed all the prescribed items and were included into the preparation rate assessment. Although the rate of excellent preparation (BBPS 9 and 8) was more frequent in Reg. 2, the rate of successful preparation (BBPS 9-6) was better following Reg. 1 (p < 0.05).

<table>
<thead>
<tr>
<th>The rate of preparation</th>
<th>Reg. 1 (n = 33)</th>
<th>Reg. 2 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 9</td>
<td>1 (3.0%)</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>- 8</td>
<td>6 (18.2%)</td>
<td>11 (35.5%)</td>
</tr>
<tr>
<td>- 7</td>
<td>16 (48.5%)</td>
<td>12 (38.7%)</td>
</tr>
<tr>
<td>- 6</td>
<td>8 (24.2%)</td>
<td>–</td>
</tr>
<tr>
<td>- 5</td>
<td>2 (6.1%)</td>
<td>4 (12.9%)</td>
</tr>
</tbody>
</table>
Discussion/Conclusion: The combination of Endofalk® with bysacodyl is better tolerated than sennosides (p < 0.05). The successful rate of preparation depends on compliance and conditions of preparation to colonoscopy, which was good and excellent following both regimes (93.9% and 87.1%, respectively), slightly better in Reg. 1 (p < 0.05).
Expression of Collagen IV is associated with neoangiogenesis and lymph node metastases in pancreatic ductal carcinoma

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death. Pancreatic cancer cells actively take part in the production of extracellular matrix proteins and caused desmoplasia called as proliferation of fibrotic tissue may conductive to tumor growth and metastasis. Histopathologically, PDAC tissue depicts dense collagen types such as I, III, IV bundles associated with fibroblasts lead to the loss of basement membrane integrity and invasion of malignant cells.

Methods: The study group consists of 57 patients diagnosed with pancreatic ductal carcinoma. Microvessel density (MVD) was counted as a number of intratumoral microvessel per unit area of the tumor, subjectively selected from the most vascularized areas (5 hpf under magnification x 40). The expression of Collagen IV was performed by immunohistochemical method and evaluated using 4-point scale: 0 lack of intratumoral stroma, 1 (weak) reaction present in < 25% of intratumoral stroma, 2 (moderate) reaction present in 25–50% of intratumoral stroma, 3 (strong) reaction present in > 50% of intratumoral stroma.

Results: Positive reaction of Collagen IV was observed in intratumoral stroma and in the basement membrane of vessels. Positive collagen IV expression was weak in 11 cases (19.2%), moderate in 16 cases (28%) and strong in 11 cases (19.2%). The expression of Collagen IV was found to correlate with lymph node involvement (p = 0.013) and MVD (p = 0.001). Mean MVD in tumor tissue was 23.25 and was associated with gender (p = 0.027) and the presence of lymph node metastases (p = 0.003).

Conclusion: Our results showed that Collagen IV is a component of intratumoral stroma in most of pancreatic ductal carcinoma cases. Moreover, it plays a significant role in an abnormal neovascularization that may lead to lymph node involvement in pancreatic ductal carcinoma patients.
Celiac disease serology in naive rheumatoid arthritis patients

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Introduction: Rheumatoid arthritis (RA) shares many clinical, epidemiological, pathophysiological, environmental and genetic aspects with celiac disease (CD).

Aim: To evaluate the CD associated serological profile in newly diagnosed RA patients.

Methods: Using the study cohort of an RA patient-centered network in Germany, we were able to test patients at the onset of their diagnosis and their follow up visits. Sera of 135 adult patients with confirmed diagnosis of RA were compared to 79 blood donors using the following ELISAs: AESKULISA® CeliCheck New Generation (for the determination of anti tTg neo-epitope IgA and IgG autoantibodies), AESKULISA® tTg Check (for in house research use only, combined IgA and IgG autoantibodies against tTg), and AESKULISA® CCP IgG.

Results: 3/135 (2.2%) RA patients tested at their 1 visit, showed elevated levels of anti tTg neo-epitope antibodies OD 0.83 ± 0.35 (p < 0.0001). However, 15/135 (11.1%) of these RA patients showed positive levels for tTg specific autoantibodies (0.61 ± 0.24, p < 0.0001) and 60% of these were seronegative for the RA marker CCP. Continued measurements in patients which were CCP serologically negative up to visit 4. Disclosed 2/15 remained positive in anti tTg autoantibodies and stayed negative in CCP.

Discussion/Conclusion: The incidences of RA and CD are similar, in the range of 1%. CD positive serology is significantly higher in RA patients, much more for anti tTg than for anti tTg neo-epitope. Both of the autoimmune diseases share clinical, epidemiological, pathophysiological, environmental and genetic aspect with celiac disease. Since both are enzymatic post translation modification of proteins, intestinal increased permeability, increased dysbiotic diversity, common environmental factors, mediated, the significance of the presence of the CD autoantibodies in RA is interesting. Is it an epiphenomenon or have a pathophysiological role? Farther studies are needed to explore and unravel this dilemma.
Factors related to low serum vitamin B$_{12}$ levels in older patients with non-atrophic gastritis in comparison to patients with normal vitamin B$_{12}$ levels

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Introduction: Vitamin B$_{12}$ deficiency is frequently seen in older patients and the main reason is pernicious anemia. The incidence of vitamin B$_{12}$ seems to increase with age and it has been reported that 15% of adults over the age of 65 have laboratory evidence of vitamin B$_{12}$ deficiency. However, vitamin B$_{12}$ deficiency can also occur in patients with non-atrophic gastritis.

Methods: The aim of this study was to investigate factors affecting serum vitamin B$_{12}$ levels in older patients with non-atrophic gastritis. 1,256 out of 1,607 patients aged over 60 who had undergone an upper gastrointestinal endoscopy for various reasons, who had serum vitamin B$_{12}$ levels and who had been diagnosed as having non-atrophic gastritis were analyzed in terms of factors responsible for low serum vitamin B$_{12}$ levels.

Results: Patients with non-atrophic gastritis were divided into two groups: patients with normal serum vitamin B$_{12}$ levels (group I, n = 759) and patients with low serum vitamin B$_{12}$ levels (group II, n = 497). The median serum vitamin B$_{12}$ level was 339 (201–987) pg/mL in group I and 180 (50–200) pg/mL in group II. The incidence of Helicobacter pylori (n = 154 vs. 325, p < 0.001), neutrophil activity (n = 176 vs. 367, p < 0.001), intestinal metaplasia (n = 35 vs. 14, p < 0.001) and inflammation (n = 230 vs. 386, p < 0.001) was significantly higher in group II than in group I. 785 patients tested negative for both H. pylori and atrophy. Of these 785 patients, the incidence of neutrophil activity (n = 56 [32.6%] vs. 25 [4.4%], p < 0.001) and inflammation (n = 69 [40.1%] vs. 82 [13.4%], p < 0.001) was significantly higher in group II than in group I. Significant differences were found between group I and group II, indicating that the mean platelet volume (MPV) was significantly higher in group I than in group II (8.7 fl [5.7–14.1] vs. 8.55 [5.8–13.1], p = 0.034). A receiver operating characteristic curve (ROC) analysis suggested that the optimum MPV cut-off point was 8.05 fl with a specificity and sensitivity of 0.75 and 0.30 respectively (Figure 2). However, there was no statistically significant difference between groups I and II in terms of PLR (124.64 [18.4–602] vs. 122.35 [11–872], p = 0.825).

Discussion/Conclusion: The incidence of H. pylori was significantly higher in older patients whose serum vitamin B$_{12}$ levels were ≤ 200 pg/mL, and H. pylori density was inversely correlated with the serum B$_{12}$ level. Chronic non-atrophic corpus gastritis is a significant cause of vitamin B$_{12}$ deficiency in older patients. Based on this study’s findings and in accordance with current guidelines, we recommend that older patients with serum vitamin B$_{12}$ levels of ≤ 200 pg/mL undergo an upper gastrointestinal endoscopic examination. Simple systemic inflammatory response markers such as MPV may be beneficial in clinical practice for the differentiation of patients with low or normal serum vitamin B$_{12}$ levels.
Comparison of three different scoring systems for risk stratification in geriatric patients with acute upper gastrointestinal bleeding

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Ankara University Faculty of Medicine, Gastroenterology, Ankara, Turkey

Introduction: Acute gastrointestinal bleeding is a potentially life-threatening condition, which requires rapid assessment and dynamic management. Several scoring systems have been established to predict mortality and rebleeding. The aim of this study was to compare three different scoring systems in order to predict short-term mortality, rebleeding rate, duration of hospitalization and need for blood transfusion in elderly patients with upper gastrointestinal bleeding.

Methods: A retrospective analysis was undertaken in 335 elderly patients with upper gastrointestinal bleeding. The pre- and post-endoscopic Rockall, Glasgow-Blatchford and AIMS65 scores were calculated, and the association between these scoring systems and patient outcomes such as rebleeding, mortality, and need for blood transfusion were assessed. The area under the receiver operating characteristic curve was calculated to assess the validity of scoring systems in predicting mortality, rebleeding, and duration of hospitalization.

Results: Pre- (4.5) and post-endoscopic (7.5) Rockall were superior to Glasgow-Blatchford (12.5) in terms of predicting mortality ($p = 0.006$, $p = 0.015$). Likewise, pre- (4.5) and post-endoscopic Rockall were superior to Glasgow-Blatchford in terms of predicting rebleeding ($p = 0.013$, $p = 0.03$). There was an association between prolonged hospitalization and mortality. 94% of patients with an average 5 days of hospitalization were alive, while the percentage reduced to 56.1% for 20 days and 20.2% for 40 days.

Discussion/Conclusion: The Rockall score is clinically useful in predicting mortality and rebleeding compared to Glasgow-Blatchford and AIMS65 systems. However, in predicting duration of hospitalization and need for blood transfusion, Glasgow-Blatchford scoring system was superior to Rockall and AIMS65 in elderly patients with upper gastrointestinal bleeding.
A rare case of fulminant pseudomembranous colitis in elderly

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Introduction: Quinolones are used with caution in the elderly because of their cardiotoxicity, neurotoxicity and musculoskeletal adverse effects. At the same time Clostridium difficile (C. difficile)-associated pseudomembranous colitis more often is also associated with quinolones. The clinical courses of pseudomembranous colitis are with different severity: from mild to severe, life-threatening forms rarely. We report a rare case of fulminant pseudomembranous colitis in the elderly associated with a quinolone therapy.

Methods: 82-year-old male. The triple therapy including proton pump inhibitor, clarithromycin and amoxicillin was initiated ambulatory to eradicate H. pylori infection. Generally, this therapy is well tolerated, with only a few and minor side effects. Failure to eradicate H. pylori occurred due to resistance to macrolide. Alternative triple-therapy regimens performed after two months. Clarithromycin was changed with ciprofloxacin 500 mg orally twice a day. On the 5th day of treatment started diarrhea. Ciprofloxacin was discontinued. However, the intensity of diarrhea containing watery stool increased. Manifested collapse and hypovolemic shock. The patient was admitted to the intensive care unit. Colonoscopy showed typical appearance of pseudomembranous colitis and the stool test for C. difficile toxins was positive. Rapid resolution of symptoms appeared with vancomycin treatment, but in the next day respiratory distress syndrome developed. Despite the measures taken mechanical ventilation and other resuscitation issues, the patient died.

Discussion/Conclusion: In the elderly the risks of development fulminant pseudomembranous colitis are increased. Fulminant pseudomembranous colitis is another reason to use quinolone antibiotics with caution for treating infections in the older age group.
Azathioprine-induced haemorrhagic gastritis

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Introduction: The purine analogues azathioprine (AZA) and mercaptopurine (MP) are the most frequently used immunosuppressives for maintaining remission of Crohn’s disease (CD) and ulcerative colitis (UC) but treatment is associated with adverse effects leading to discontinuation of treatment in up to 30% of patients. Adverse events are classified as ‘dose-dependent’, such as myelotoxicity and ‘dose-independent’; the latter are either due to allergic reactions (rash, flu-like symptoms) or to idiosyncratic reactions (pancreatitis, hepatitis). Haemorrhagic gastritis is not listed in AZA-induced adverse events (FDA). A search in PubMed did not extract any report associating ‘azathioprine’ and ‘gastritis’ (or ‘haemorrhagic gastritis’).

Case series: This is a report on 9 patients (6 men) of median age 19 (18–25), 5 with CD (ileitis or ileocolitis; 2 patients with perianal involvement), who received AZA for steroid-dependent IBD. TPMT was available in 3 patients and was reported in the normal range. Five patients were co-treated with tapering doses of conventional corticosteroids or budesonide. None was alcohol imbiber and only 5 were smokers. All patients had a baseline gastroscopy, which showed a normal upper gastrointestinal system and no H. pylori infection. After a median dose of 75 mg (range 50–125 mg) AZA for a median period of 15 days (range 9–18 days), patients were admitted to the hospital urgently with epigastric and/or abdominal pain, low grade fever, and haematemesis. Physical examination, revealed no signs except from mid-epigastric tenderness on palpation. Laboratory tests revealed marked leukocytosis with a left switch but no abnormal liver function tests, LDH, lipase or amylase. Upper abdominal ultrasound did not reveal any abnormal findings. Emergency gastroscopy showed blood in the gastric lumen, excessive mucosal oedema, erythema, haemorrhagic petechiae, exudate and aphthous ulcers throughout the gastric body and antrum. The oesophagus and the duodenum were normal. Histology revealed a severe and confluent acute inflammatory infiltrate consisting of neutrophils eosinophils and dilated vascular vessels. No H. pylori, cytomegalovirus, Herpes virus, or any other infectious agents were detected. In most cases, administration of esomeprazole, ciprofloxacin, metronidazole, and occasional i.v. administration of hydrocortisone resulted in rapid resolution of symptoms and dramatic improvement in the endoscopic picture after 5 (4–7) days. Re-challenge with AZA resulted in rapid recurrence of symptoms. Most of the patients were treated with anti-TNF agents or methotrexate without any recurrence of symptoms. It must be noted that 3 patients have tolerated MP later in the disease course.

Conclusion: Haemorrhagic gastritis is not a recognized adverse event of AZA. We believe that AZA was the responsible agent because as it was developed soon after initiation of AZA, was followed by rapid resolution of symptoms and/or endoscopic signs after AZA withdrawal, and in some patients recurred after re-challenge.
The stressometer: A simple, valid and responsive measure of psychological stress in inflammatory bowel disease patients

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Introduction: Psychological stress is associated with inflammatory bowel disease (IBD), but the nature of this relationship is complex. At present, there is no simple tool to screen for stress in IBD clinical practice or assess stress repeatedly in longitudinal studies. Our aim was to design a single question “stressometer” to rapidly measure stress and validate this in IBD patients.

Methods: 304 IBD patients completed a single question “stressometer”. This was correlated with stress as measured by the Depression Anxiety Stress Scales (DASS-21), quality of life and disease activity. Test-retest reliability was assessed in 31 patients who completed the stressometer and the DASS-21 on two occasions four weeks apart.

Results: Stressometer levels correlated with the DASS-21 stress dimension in both Crohn’s disease (CD) (Spearman’s rank correlation coefficient [rs] 0.54; p < 0.001) and ulcerative colitis (UC) (rs 0.59; p < 0.001). Stressometer levels were less closely associated with depression and anxiety (rs range 0.36–0.49; all p values < 0.001). Stressometer scores correlated with all four Short Health Scale quality of life dimensions in both CD and UC (rs range 0.35–0.48; all p values < 0.001) and with disease activity in Crohn’s disease (rs 0.46; p < 0.001) and ulcerative colitis (rs 0.20; p = 0.02). Responsiveness was confirmed with a test-retest correlation of 0.43 (p = 0.02).

Discussion/Conclusion: The stressometer is a simple, valid and responsive measure of psychological stress in IBD patients and may be a useful patient reported outcome measure in future IBD clinical and research assessments.
Hypovitaminosis D: A harbinger of biochemical non-response in primary biliary cirrhosis

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²NIHR Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham, UK

Introduction: Hypovitaminosis D is frequently found in patients with PBC and is associated with symptomatic disease. Given the anti-inflammatory and antifibrotic effects of vitamin D, we sought to investigate the association of vitamin D with presentation and course of PBC.

Methods: We performed a retrospective analysis of patients attending the Jena University Hospital for treatment of PBC. 25-hydroxyvitamin D [25(OH)D] levels were determined by routine laboratory analysis and response to UDCA was evaluated by Paris-I criteria after 12 months.

Results: Among 227 patients treated for PBC, serum levels of 25(OH)D prior to the initiation of UDCA were available from 43 patients with PBC. Forty-one (95%) were female and the median age at presentation was 53 years (range 35–78). Twenty-nine (67%) patients tested positive for anti-nuclear antibodies (ANA), of which 14 exhibited a multiple nuclear dot staining pattern or were positive for PML or Sp100 antibodies by immunoblotting. Serum 25(OH)D concentrations at baseline were normally distributed with a mean (± s.d.) of 22(± 11) ng/mL and negatively correlated with serum bilirubin and with aspartate aminotransferase (AST) but not with alkaline phosphatase. 25(OH)D concentrations were lower in patients with ANA-positivity. Low 25(OH)D serum levels were associated with elevated AST to platelet ratio index (APRI) at baseline and predicted 12-month biochemical non-response to UDCA (Paris-I criteria).

Discussion/Conclusion: Low vitamin D levels in PBC were associated with advanced disease, poor UDCA response and surrogates of adverse events in this retrospective study. Vitamin D supplementation may serve as a promising strategy to improve hepatic immune tolerance, thereby reducing biliary injury and subsequent fibrosis in PBC.
Steroid-refractory or complicated Crohn's disease? Is the diagnosis right?

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Introduction: In the case of fever or deterioration of general condition of IBD patients taking immunosuppressives it is essential to search for infection. If it is excluded, therapy refractory disease as well as the revalidation of the diagnosis should be considered.

Case report: A 57-year-old malnourished male patient was admitted to our hospital because of long standing diffuse abdominal pain, bloatedness, diarrhea, weight loss and iron deficiency anemia. Abdominal ultrasound showed thickening of the wall of the right colon and chest X-ray showed a nodule in the right upper lobe. As the chest CT raised the possibility of tuberculosis the patient was referred to the pulmonologist, who excluded active disease. Abdominal CT revealed inflammation of the coecum and ileum associated with mesenteric lymphadenomegaly that proposed the diagnosis of Crohn's disease. The macroscopic appearance of the mucosa seen during colonoscopy was also suspicious to inflammatory bowel disease. Histological examination described unspecific ulcerated lesions of the mucosa. As the diagnosis of Crohn's disease was raised, mesalazine and oral steroid therapy was started. During the treatment fever occurred which declined by antibiotic therapy and by switching to intravenous steroid. Regarding of the patient's severe malnutrition and inadequate oral intake of nutrients supplementary parenteral nutrition was necessary to start. Despite of long-term and complex treatment there was no remarkable improvement in the general condition of the patient. It made us to review the former results and ask for additional histological examination, which revealed infectious origin of the disease.

Conclusion: If the diagnosis of Crohn's disease is uncertain as well as refractory disease is suspected other cause of the intestinal inflammation and complication of the therapy should be investigated which can be challenging in the case of atypical infection.
Concentration of soluble selectins (sP-, sE-, sL-) in colorectal cancer

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Introduction: Tumor cells interact with platelets and leukocytes, which protects them from the immune system and allows to formation of metastases. Selectins mediated cell adhesion to the endothelium and allow their transmigration into the extravascular space. It is suggest that the interaction between selectins and their ligands on tumor cells and endothelial using the same mechanisms as the binding of inflammatory cells. The aim of this study was to evaluate the concentration of sP-, sE- and sL-selectin in patients with colorectal cancer. The relationships between the stage of disease and location of the tumor in the colon were also assessed.

Material and Methods: The study was conducted in 53 patients (24 women and 29 men, average age 66.9) with colorectal cancer and in 25 healthy subjects. The study group was divided into three subgroups: I - TmN0M0, II - TmN+M0 and III - TmN+M+ and due to the tumor localization: colon, sigmoid colon and rectum. The levels of soluble selectin were measured using the ELISA kits (R&D Systems).

Results: Significantly higher levels of sP-, sE- and sL-selectin (respectively 74.29 ng/ml, 35.60 ng/ml, 952.32 ng/ml) were showed in patients with colorectal cancer as compared to healthy subjects (respectively, 40.62 ng/ml, 26.74 ng/ml, 825.56 ng/ml) (p < 0.001). sP-selectin concentration was highest in group III in comparison with group I and II (p = 0.01), sE-selectin in group II comparison with group I (p = 0.03), while level of sL-selectin was not correlated with TNM. The level of sE-selectin was highest in patients with sigmoid cancer (p = 0.02). Concentration of sL- and sP-selectin was not correlated with tumor localization. The area under the ROC curve shows the highest diagnostic power of sP-selectin (AUC = 0.887).

Conclusions: High levels of sP- and sE-selectin indicate activation of platelets and endothelial cells in colorectal cancer. Increase in the level of these proteins with metastases may indicate their potential role in cancer progression.
KID: A database of capsule endoscopy images and videos with paired annotations for developing automatic recognition software

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Introduction: Wireless capsule endoscopy (WCE) has opened up the path of a minimally-invasive approach in digestive endoscopy. Nevertheless, WCE videos review remains a tedious clinical task. Several algorithms for automatic lesion detection and localization have been proposed [1]. However, the limited availability of annotated WCE data is a barrier for further progress [2]. KID, a recently- launched multimedia database, aims to become the reference standard for the evaluation of intelligent WCE software.

Methods: KID (http://is-innovation.eu/KID) is a tool for software research in WCE; it, can accommodate anonymised images, video clips and/or full WCE videos from commercially available capsule models. Image/lesion categorisation is based on Capsule Endoscopy Structured Terminology (CEST) [3]. Lesions annotations, indicating the accurate location/size of abnormalities, is a major feature. Annotations are supported by an open access annotation tool (Ratsnake) [4]. Images and video files contributed to KID should be of high quality, preferably at original resolution; recommended standard for image & video contributions are ISO/IEC 15948 PNG (Portable Network Graphics) and ISO/IEC 14496-10 MPEG-4 AVC (Advanced Video Coding), respectively.

Results: More than 1,500 annotated WCE images, several video clips and videos have been registered in KID since it became operational in September 2014. The database now includes normal as well as WCE images of lesions. A WCE image dataset from KID has already been used for lesion detection software development [5]. KID is also able to accommodate video clips from in vitro and ex vivo experimentation on localisation software [6] as well as images that may be obtained with hyperspectral imaging [7]. Therefore, combination of various technological bricks from different scientific areas that can be used for next generation of WCEs, can be accommodated in KID [7].

Discussion/Conclusion: We present KID, a public multimedia database that is able to become the gold standard tool to assess the performance of software research work in the field.
References:

Evaluation of prealbumin and retinol binding protein as severity markers during an episode of acute pancreatitis

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Introduction: Prealbumin (known as transthyretin) and retinol binding protein (RBP) are biochemical markers of protein energy malnutrition. However, regard the acute phase response prealbumin together with transferrin, albumin and RBP are referred to negative acute phase proteins unlike CRP, which is positive acute phase protein. Hypoalbuminemia is valid negative prognostic factor. Albumin has a longer half-life compared to prealbumin and RBP. Our aim was to evaluate the potential role of prealbumin and RBP for severity and SIRS prediction in patients during episode of acute pancreatitis (AP).

Methods: Study encompassed 40 patients (20 male), mean aged 49 years, who consented to participate; 17 patients suffered from recurrent chronic pancreatitis and 23 from first episode of AP. Alcohol abuse was most common etiology (31 patients). AP severity was assessed by Revised Atlanta criteria (mild, moderate, severe). Serum prealbumin levels (normal ranges: 0.2–0.4 g/L) and RBP (normal ranges: 0.03–0.06 g/L) were measured in addition to routinely used hematological and biochemistry analyses by immunonephelometry assay between first 24 and 48 hour of admission. Statistical analysis was performed via SPSS vs. 19.

Results: Mean ± SD prealbumin for all patients was 0.188 ± 0.11 g/L and RBP 0.036 ± 0.03 g/L. Mild AP was established in 32% with mean values of prealbumin 0.24 ± 0.11 g/L and RBP 0.06 ± 0.03 g/L in this group; moderate AP in 42% (mean prealbumin: 0.19 ± 0.11 g/L and RBP: 0.028 ± 0.03 g/L) and severe in 26% (mean prealbumin: 0.12 ± 0.11 g/L and RBP 0.023 ± 0.02 g/L). There was a statistically significant difference between severity of AP and decreased levels of prealbumin and RBP as well as between groups with and without SIRS (p < 0.05).

Discussion/Conclusion: Decreased prealbumin and RBP levels are observed by severe complicated AP and SIRS. These are potentially useful markers for routine practice and could facilitate monitoring patients’ recovery and adequacy of early nutritional re-feeding.
Upper gastrointestinal cancer mortality trend in Albania

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Introduction: Albania is a Mediterranean country where mortality from esophageal cancer (EC) is relatively low and a developing country where mortality from EC is relatively high. Also, the high rate of Helicobacter pylori seroprevalence in the Albanian population may be the primary risk factor for gastric cancer (GC) in Albania [1]. Therefore, it seemed of interest to investigate the mortality from upper gastrointestinal (GI) cancer (EC and GC) in Albania (a high and low-risk area).

Methods: We analyzed official death certification data of EC and GC collected from the Institute of Statistics of the Republic of Albania (International Classification of Diseases, 9th revision, code 150 and 151) during the period 2006–2010. Age-standardized mortality rates per 100,000 inhabitants were calculated by sex and age groups and the trend analyses was evaluated as annual percent change (APC).

Results: During the study period, 1682 upper GI cancer deaths were registered in Albania (9.5% of all deaths due to malignant tumors). Overall, upper GI cancer mortality was 9.8, 7.8, 8.5, 7.6 and 6.4 for the years 2006, 2007, 2008, 2009 and 2010, respectively. The upper GI cancer mortality decreased with a significant linear trend for both EC and GC (APC = -1.2, 95% CI: 0.9–1.5% and APC = -2.1, 95% CI: 1.9–2.5%, \( p < 0.001 \), respectively), but with no statistical significance between genders. However, mortality rates varied between age groups where an increasing not significant trend was reported in the youngest age group (APC = 1.9% at age 20–49, \( p \) trend = 0.59) whereas a decreasing not significant trend was observed in the middle-aged group and the oldest age group (APC = -9.2% at age 50–69, \( p \) trend = 0.18 and APC = -8.7% at age 70–79, \( p \) trend = 0.12, respectively).

Conclusion: In Albania, a developing country and area with higher H. pylori infection, upper GI cancer mortality showed a predominant decline with different pattern between age groups. It may be concerned with the change in epidemiological factors in the mortality of upper GI cancer that needs further studies.

Reference:

Anti-neo-epitope tTg complexed to gliadin are more reliable then tTg for celiac disease diagnosis

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Introduction: The guidelines of ESPGHAN for the diagnosis of pediatric celiac disease (PCD) rely on anti-human tissue transglutaminase (tTg) as the prime and unique antibody for screening PCD population. None of the CD-associated antibodies has challenged tTg premiership. tTg complexed to gliadin presents neo-epitopes and antibodies against the complex are called tTg neo-epitope (tTg-neo). Reliability of anti-tTg and tTg-neo antibodies in diagnosis of PCD was compared.

Methods: 95 pediatric CD patients (mean 8.3 y), 99 normal children (NC) (8.5 y) and 79 normal adults (NA) (28 y) were tested using the following ELISAs detecting IgA, IgG or both IgA and IgG: AESKULISA® tTg (tTg; RUO) and AESKULISA® tTg New Generation (Neo-epitope tTg complexed to gliadin). The results were compared to the degree of intestinal injury, using revised Marsh criteria.

Results: A significantly higher OD activity was detected for tTg-neo IgA, IgG and IgA + IgG than for tTg (p < 0.0001, p < 0.0001, p < 0.001, respectively). tTg-neo IgA, IgG correlated better with intestinal damage than tTg (r² = 0.968, 0.989 compared to 0.909, 0.488 [p < 0.001], respectively).

The tTg-neo IgA, IgG and IgA + IgG isotypes exhibited a higher OD activity and better reflected intestinal damage in PCD, compared to tTg isotypes. The tTg-neo combined IgA + IgG ELISA kit had higher sensitivity and a comparable specificity for the diagnosis of childhood CD.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
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<td>tTg-neo IgA + IgG</td>
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<td>98.99</td>
<td>98.91</td>
<td>96.08</td>
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<tr>
<td>tTg IgA + IgG</td>
<td>83.16</td>
<td>100</td>
<td>100</td>
<td>86.0</td>
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<tr>
<td>Significance</td>
<td>p &lt; 0.0001</td>
<td>0.0001</td>
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</tr>
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</table>

PPV = positive predictive value; NPV = negative predictive value

Discussion/Conclusion: tTg neo should be included in the ESPGHAN diagnostic flow chart.
The annual incidence/prevalence of autoimmune diseases is increasing worldwide

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Introduction: A steady rise in autoimmune disease (AD) throughout westernized societies over the last three decades is suggested. Multiple publications exist, however, long term comparison studies on selected populations are scarce.

Aims: To calculate the % increases per year of AD frequencies worldwide, analyze the differential increases of AD per country and disease, and identify geoepidemiological trends.

Methods: Studies from the last 30 years were identified using Medline, PubMed, Google, and the Cochrane Library databases. Only long-term regional or national longitudinal follow-ups are reported.

Results: The means ± s.d. of the net % increased/year incidence and prevalence of ADs worldwide were 6.1 ± 4.9 and 11.2 ± 12.8, respectively. Neurological (myasthenia gravis, multiple sclerosis), gastrointestinal (celiac disease, Crohn’s disease and IBD), endocrinological (IDDM, autoimmune thyroiditis) and rheumatic (SLE, SARD, RA) ADs, revealed the following trends: 14.3, 6.24, 5.19 and 3.7 net % increases, respectively. The highest net % increase per year was noted in the neurological followed by gastrointestinal, endocrine, and rheumatic diseases. Differences between old vs new frequencies were highly significant (p < 0.0001). Geoepidemiologically, high to low % increases/year of AD frequencies was: Israel, Brazil, USA, Sweden, Serbia, Canada, Denmark, UK, Finland, Italy, Norway and Japan with 16.7, 11.1, 11.1, 8.3, 6.7, 6.6, 5.6, 5.5, 4.3, 4.0, 3.1 and 3.0%, respectively. Comparing old to new surveys in various countries demonstrated net % increase rates, in a decreasing order: celiac disease, Crohn’s disease, autoimmune thyroiditis, autoimmune hepatitis, bullous pemphigoid, multiple sclerosis, insulin-dependent diabetes mellitus and intestinal bowel disease. Incidences and prevalences of ADs have increased significantly over the last 30 years. Neurological (MS), gastrointestinal (CD, IBD) ADs and the countries: Israel, Brazil and USA increased the most.

Discussion/Conclusion: These observations point to a stronger influence of environmental factors as opposed to genetic factors on AD development.
Immunomodulatory properties of antibiotics in DNBS-colitis: Micro-RNA expression and gut microbiota diversity

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Introduction: Minocycline and doxycycline exert immunomodulatory effects that could be beneficial in IBD. Micro-RNAs have been recently reported to play a key role in intestinal homeostasis that can be influenced by microbiota populations. The aim of the study was to evaluate the effect of these antibiotics in the DNBS-colitis model in mice, characterizing the modifications induced in the micro-RNA expression and bacterial diversity.

Methods: Male CD1 mice were assigned into non-colitic and DNBS-colitic groups. Colitis was induced by DNBS intracolonically (4 mg/mouse). Once the colitis process was established, colitic mice were divided in three groups: DSS-control (without treatment), MNC (receiving minocycline 50 mg/kg/day) and DXC (receiving doxycycline 10 mg/kg/day). The inflammatory status was evaluated by a colonic weight/length, qPCR of inflammatory markers, including micro-RNAs. Also, changes in microbiota populations and biodiversity were characterized by pyrosequencing.

Results: According to the macroscopic results, minocycline and doxycycline treatment improved the recovery of colitic mice, ameliorating some of the inflammatory markers, including MMP-9, MUC-3, occluding, TNF-α and ICAM-1. A micro-RNA expression profile was established for this model of colitis showing an increased expression of miR-223 and miR-9 while miR-150 were decreased. Both antibiotics partially restored the expression of some of these markers. Pyrosequence characterization of microbiota showed that minocycline and doxycycline treatments increased the bacterial diversity, reverting the dysbiosis produced by DNBS-colitic and increasing the biodiversity.

Discussion/Conclusion: Minocycline and doxycycline are able to modify the expression of different inflammatory markers and microRNAs, as well as to increase the intestinal bacterial diversity. These observations confirm the combined contribution of antibiotic and immunomodulatory properties ascribed to these compounds that could be of great interest to control the complex pathogenesis of IBD.
Vitamin D in cirrhotic patients with an infection

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Recently, progress has been made in understanding how the noncanonical activities of vitamin D influence the pathogenesis and prevention of human disease. In our study concentrations of serum 25OHD were significantly associated with infections in cirrhotic patients. Probably vitamin D stores may influence susceptibility to infection in individuals through the vitamin D receptor and some vitamin D-dependent inducible bactericidal antimicrobial peptides such as cathelicidin and others. As more knowledge accrues, vitamin D supplementation may someday be useful as adjuvant therapy in patients with infections.

Introduction: Novel insights into additional roles for vitamin D are being established. Some nontraditional roles ascribed to vitamin D include anti-inflammatory and immune-modulating effects.

Methods: Concentrations of 25OHD (metabolite of vitamin D) were measured from 20 age-, sex-, race-, and season-matched patients with liver cirrhosis from prospective study. Optimal 25OHD status ranges from 50 to 100 nmol/l (expert opinion).

Results: 20 middle-aged (46.9 ± 13.6 yrs old, 55% men) cirrhotic inpatients Child-Pugh class B/C (5/15) were included. 15 (75%) were admitted with an infection. Concentrations of 25OHD < 50 nmol/l was detected among 65% cirrhotic patients, 80% patients Child-Pugh class B, 60% - C, 74% cirrhotic patients with an infection, 40% cirrhotic patients without any infection. Significantly more patients with decreased level of vitamin D developed infections (p = 0.0004).

Discussion/Conclusion: Prevalence patients with liver cirrhosis (65%) had decreased concentrations of 25OHD. The concentrations of 25OHD <50 nmol/l were not associated with a class of severity liver cirrhosis according Child-Pugh score and were associated with an increased risk of bacterial infections in liver cirrhosis patients. Further characterization of vitamin D will help elucidate the pathogenesis of various human diseases and in the design of new approaches for prevention and treatment.
Regulation of colitis-associated cancer development via HIF1α activation in myeloid cells

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Introduction: Inflammatory bowel diseases are an important risk factor for development of colon cancer, but the molecular mechanisms are still being uncovered. Inflammatory signaling and immune cell infiltration secondary to hypoxia are clear drivers of tumor progression. We analysed the functional relevance of hypoxia transcription factor-1 (HIF1) in myeloid cells for colitis-associated cancer (CAC) development.

Methods: Wildtype and HIF1αΔMC mice (HIF1α-deficient mice in myeloid cells) were exposed to AOM+DSS model. HIF1 activation was evaluated with western blot analysis, immunohistochemistry, and RT-qPCR for HIF1 target genes. Tumor growth was analyzed using endoscopy. HIF1-dependent pathway activation was evaluated with RNA-seq and gene set enrichment of differentially expressed genes.

Results: Tumors induced by AOM+DSS model in wildtype mice showed an upregulation of HIF1 target-genes and increased expression of HIF1 alpha subunit upon immunohistochemistry. Immunohistochemistry revealed strong tumor infiltrating macrophages. The HIF1αΔMC mice exposed to AOM+DSS showed attenuated tumor growth compared to control mice. There was no difference regarding intestinal inflammation between both groups. Accordingly, no difference was found regarding the number of tumor infiltrating macrophages and neutrophils between HIF1αΔMC and control mice. Gene set enrichment identified several pathways regulated by HIF1 in myeloid cells. Subsequent analysis could show that HIF1 activation in myeloid cells promotes M2 polarization and thereby leads to an inhibition of the anti-tumor immune response.

Discussion/Conclusion: In summary, HIF1 activation in myeloid cells seems to be involved in the regulation of immune cell infiltration and the activation of several pathways critical for tumor growth thereby providing a tumor-promoting pro-inflammatory microenvironment. Therefore, therapeutic strategies targeting HIF-dependent pathways might provide a future option for the prevention or treatment of CAC in IBD patients.
Inhibition of mitochondrial Lon protease induces an apoptosis in the primary hepatocellular carcinoma cells

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Introduction: Expression of the ATP-dependent mitochondrial protease Lon is elevated in the cells of hepatocellular carcinoma (HCC) as we found in our previous work. Also we have shown that Lon is connected with mitochondrial mTOR kinase. Next phase of our work was to induce an apoptosis using the anti-Lon antibodies.

Methods: The samples of HCC (n = 9) and comparable non-cancer liver tissues (n = 9) were obtained after surgical operation. Tissues were sliced and treated by enzymes to receive the cell suspensions. Isolated cells were washed, cultured 3h in the complete DMEM medium with 20% FCS, washed again, and incubated with monoclonal antibodies. Rabbit polyclonal anti-Lon antibodies were received by co-author Rotanova. Expression of proteins was measured using western blot, Immunohistochemistry, and flow cytometry. Apoptosis was analyzed with DNA-binding dyes.

Results: Isolated HCC cells as well as normal liver cells were analyzed concerning a spontaneous apoptosis. After that cells were treated by C2-ceramide to measure an induced apoptosis. Other portions of cells were incubated with anti-Lon antibodies which induced well documented level of apoptosis in the HCC cells in all analyzed samples that was considerable greater compared with normal liver cells. Additional cell treatment with anti-mTOR mAb added simultaneous with anti-Lon antibodies raised an apoptosis in a moderate percentage. Supplement of anti-Lon antibodies by C2-ceramide led to the greater apoptosis in the case of high dose of sphingolipid. Expression of the mitochondrial apoptosis-related proteins indicates the strong involvement of mitochondria in the HCC cells apoptosis.

Discussion/Conclusion: Inhibition of mitochondrial Lon protease by antibodies leads to the HCC cell apoptosis in the high percentage that may be amplified by anti-mTOR antibodies or by treatment with C2-ceramide.
Effective ways to overcome the refractory gastroesophageal reflux disease

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Searching perspective treatment agents for gastroesophageal reflux disease (GERD) is associated with the important problem resolve – optimize the tactics of treatment the patients with refractory GERD, the frequency of which is growing rapidly.

Increasing the dose of proton pump inhibitor (PPI) in 2 times is insufficient in 15% of GERD patients, which requires improving the existing treatment standards.

The aim – to increase the treatment effectiveness of patients with refractory GERD by optimizing treatment complexes.

The study involved 38 patients with refractory GERD non-erosive form aged 29 to 57 years, depending on the treatment complexes they were divided into two groups: I (n = 18) – pantoprazole 40 mg 2 times a day, II (n = 20) – pantoprazole 40 mg 2 times a day and ursodeoxycholic acid (UDCA) 250 mg 2 times a day. The total duration of treatment was 16 weeks. Fibrogastroduodenoscopy (FGDS) was done to all the patients during the treatment every 4 weeks, and a daily assessment of the clinical status according to the Likert scale. Refractory was determined after 12 weeks in the treatment of double-dose PPI, while maintaining clinical and/or endoscopic signs of GERD.

The achievement of clinical and endoscopic remission was found after 12 weeks in 12 (66.6%) patients from group I with PPI treatment and in 17 (85%) patients of group II during PPI and UDCA treatment. Administration of UDCA in combination with proton pump inhibitors in non-erosive GERD patients with the refractory to PPI therapy significantly increases the effectiveness of long-term PPI monotherapy (p < 0.05).

Conclusion: The administration of UDCA at a daily dose of 500 mg in two divided doses on the background of a long-term PPI therapy in patients with non-erosive GERD is more effective in achieving the clinical and endoscopic remission than PPI monotherapy.
Industrial food additive microbial transglutaminase is immunogenic in children with celiac disease

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Introduction: Microbial transglutaminase (mTg) is capable of cross-linking numerous molecules. It is a family member of human tissue transglutaminase (tTg), involved in CD. Despite declarations of mTg safety, direct evidence for immunogenicity of the enzyme is lacking.

Methods: The serological activity of mTg, tTg, gliadin complexed mTg (mTg neo-epitope) and gliadin complexed tTg (tTg neo-epitope) were studied in: 95 pediatric celiac patients (CD), 99 normal children (NC) and 79 normal adults (NA). Sera were tested by ELISAs, detecting IgA, IgG or both IgA and IgG: AESKULISA® tTg (tTg), AESKULISA® tTg New Generation (tTg neo-epitope [tTg-neo]), microbial transglutaminase (mTg) and mTg neo-epitope (mTg-neo). Marsh criteria was used for the degree of intestinal injury.

Results: Comparing pediatric CD patients with the 2 normal groups: mTg-neo IgA, IgG and IgA + IgG antibody activities exceed the comparable mTg ones (p < 0.0001). All mTg-neo and tTg-neo levels were higher (p < 0.001). tTg IgA and IgG + IgA were higher than mTg IgA and IgA + IgG (p < 0.0001). The levels of tTg-neo IgA/IgG were higher than tTg IgA/IgG (p < 0.0001). The sequential antibody activities, reflecting best the increased intestinal damage, going from M0 to M3c were: tTg-neo IgG ≥ mTg-neo IgG > mTg-neo IgA + IgG > tTg-neo IgA. Taken together, mTg-neo IgG and tTg-neo IgG correlated best with intestinal pathology (r² = 0.989, r² = 0.989, p < 0.0001, p < 0.0001, respectively).

Discussion/Conclusion: mTg is immunogenic in children with CD and by complexing to gliadin its immunogenicity is enhanced. Anti-neo-epitope mTg antibodies correlate with intestinal damage to the same degree as anti-tTg. Further studies are needed to explore the pathogenic potential of anti-mTg antibodies in CD.
DNA methylation profiling in inflammatory bowel disease: New insights into disease pathogenesis and activity

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Introduction: Inflammatory Bowel Diseases (IBDs) are heterogeneous disorders with complex aetiology. Quantitative genetic studies suggest that only a small proportion of the disease variance observed in IBD is accounted for by genetic variation, indicating a potential role for differential epigenetic regulation in disease aetiology. The aim of this study was to assess genome-wide DNA methylation changes specifically associated with Ulcerative Colitis (UC), Crohn’s Disease (CD) and IBD activity.

Methods: DNA methylation was quantified in peripheral blood mononuclear cells (PBMCs) from 149 IBD cases (61 UC, 88 CD) and 39 controls using the Infinium HumanMethylation450 BeadChip. In addition, cross-tissue replication of the top differentially methylated probes (DMPs) was tested in colonic mucosa tissue samples obtained from paediatric IBD cases and controls.

Results: A total of 3196 probes were differentially methylated between CD cases and controls, while 1481 probes were differentially methylated between UC cases and controls. Moreover, pathway analysis identified enrichment of DMPs in the vicinity of genes associated with molecular pathways integral to IBD pathogenesis. There was considerable (45%) overlap between UC and CD DMPs. The top-ranked IBD-associated PBMC differentially methylated region (promoter region of TRIM39-RPP2) was also significantly hypomethylated in colonic mucosa from paediatric UC patients. We confirmed TRAF6 hypermethylation using pyrosequencing and found reduced TRAF6 gene expression in PBMCs of IBD patients.

Discussion/Conclusion: Our data provide new insights into differential epigenetic regulation of genes and molecular pathways, which may contribute to the pathogenesis and activity of IBD.
Evaluation of the Lactobacillus fermentum in the DCA experimental model of irritable bowel syndrome: Impact on anxiety behavior

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Introduction: At present, there is no ideal treatment for IBS that combines efficacy and safety. The use of alternative medicines is becoming attractive for many patients. In this study the effects of Lactobacillus fermentum was evaluated in a rat IBS experimental model induced by intracolonic administration of deoxycholic acid (DCA).

Methods: Male Sprague Dawley rats (240–320 g) were administered DCA once daily on 3 consecutive days, and received orally the probiotic (10⁹ CFU per day) or Gabapentin (70 mg/kg). One and two weeks after, abdominal withdrawal reflex to colorectal distension (CRD) was semiquantitatively scored. Also the referred pain was evaluated with von Frey filaments. After two weeks, the open field test was performed to evaluate the stress associated to IBS in a novel environment. Then, all rats were sacrificed and the expression of disease markers were evaluated in the colonic tissue by qPCR: COX-2, the mucins MUC-2 and MUC-3, and the toll like receptor TLR-3.

Results: The probiotic treated group showed lower CRD score values than IBS control, and also an amelioration of the referred pain. The open field test revealed that rats from IBS control group presented an altered behavior (decreased general activity) in comparison with normal rats, and the administration of the probiotic resulted in a restoration of the locomotor activity. The biochemical analysis of the colonic specimens revealed that Lactobacillus fermentum ameliorated the increased expression of COX-2, as well as that related with the toll like receptors TLR3. In addition, Lactobacillus fermentum was able to significantly counteract the reduced expression of the mucins, MUC-2 and MUC-3.

Discussion/Conclusion: Lactobacillus fermentum exerts beneficial effects in this experimental model of IBS, together with an improvement of the stress associated with IBS. In addition, the probiotic was able to improve the altered immune response observed in IBS.
Low molecular weight dextran sulfate nanocapsules as inhibitors of *Helicobacter pylori* adhesion to gastric cells: An alternative therapy for *Helicobacter pylori* infection

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**Introduction:** The treatment of the hostile *Helicobacter pylori* infection is facing increasing alarming antibiotic resistance worldwide which leads to failure of its eradication. This calls for alternative strategies to the use of antibiotics. The use of polysaccharides as potential therapeutic tools in the treatment or prevention of bacterial infection is recognized. Some of them are known to inhibit bacterial colonization by blocking specific carbohydrate-receptors involved in host-bacteria interaction. In addition, due to their mucoadhesive properties, polysaccharides are optimum building blocks for polysaccharide-based nanoformulations as tools to improve the local anti-*H. pylori* therapy in the mucus layer. To this end, novel antibiotic-free colloidal particles coated with mucoadhesive polysaccharide were developed as potential novel approach against *H. pylori* (solicitude of patent N. MX/a/2015/006991) which interfere with the adhesion mechanisms and thus prevent the onset of the infection and its recurrence.

**Methods:** Oil-core nanoemulsions co-stabilized with lysozyme and lecithin were prepared. These nanoemulsions have a neutral charge and allow the consequential deposition of negatively charged polysaccharides without the use of synthetic cationic surfactant. Nanocapsules were prepared by coating the nanoemulsion with dextran sulfate of either low-\(M_w\) (DexS40) or high-\(M_w\) (DexS500). The antiadhesive effect was quantified by FACS measuring the amount of FITC-labeled *H. pylori* attached to AGS cells after pretreatment with various formulations.

**Results:** The formulations comprising low-\(M_w\) DexS40 nanocapsules were able to reduce, in a dose-dependent way, the adhesion of *H. pylori* to AGS cells. The overall magnitude of inhibition was greater than that of DexS500 nanocapsules and uncoated ones. Moreover, the same amount of polysaccharides in free solution did not display any antiadhesive effect.

**Discussion/Conclusion:** We obtained the proof-of-concept that polysaccharide-based nanocapsules were able to reduce, in a dose-dependent way, the adhesion of pre-treated *H. pylori* to AGS cells. We speculate on the potential use of these nanocapsules as prophylactic therapy to prevent the re-infection with *H. pylori*. 
The modulation of tumor growth and inflammation by metformin treatment in colitis associated cancer

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Introduction: Although the increased risk for colorectal cancer in patients with inflammatory bowel disease is well known, the underlying mechanisms remain to be clarified. Metformin is used for treating diabetes type 2 and has been recently reported to provide anti-inflammatory effects, which could reduce the risk of CRC in IBD patients. In this study, we investigated the effect of metformin on colitis-associated cancer (CAC).

Methods: Wildtype mice were exposed to the azoxymethane (AOM) and dextran sulfate sodium (DSS) model of CAC. Tumor growth and inflammation were analyzed using mini-endoscopy at repeated time points. Additionally, the effect of metformin on tumor cells was assessed in vitro using MC38, HTC116 and SW480 colorectal cancer cell lines treated with metformin in different concentrations (0 mM, 0.5 mM, 1 mM, 2.5 mM, 5 mM, 7.5 mM and 10 mM). Western blot, immunohistochemistry and RT-qPCR analysis were used to evaluate the expression of important proteins and genes involved in the pathophysiology of CAC.

Results: Mice treated with metformin showed reduced inflammation and tumor growth in the AOM + DSS model checked by colonoscopy and histological analysis. Likewise, in vitro experiments demonstrated a decrease of cell proliferation of all tumor cell lines after metformin treatment evaluated by xCELLigence System and WB for cyclin D1.

Discussion/Conclusion: Metformin is widely used for treatment of diabetes and also seems to have promising therapeutic properties against the development of colitis-associated cancer. Although the mechanisms by which metformin modulates inflammation and cancer require further investigations, our data provide new insight into the chemopreventive and anti-cancer properties of metformin.
**Nitrates pollution as a possible risk factor for digestive cancer**

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Several epidemiological and experimental studies estimate that nitrates/nitrites/ N-nitroso compounds are involved in etiology of digestive cancer.

**Introduction:** Aim of our study was to correlate the prevalence of digestive cancers in rural communities in south-west of Romania (a region with extensive agriculture) and the nitrates pollution level of well water. The nitrates concentrations values are influenced by the soil profile, the amounts of mineral fertilizers used and the level of precipitations.

**Methods:** The nitrates/nitrites concentration was measured using the phenol-disulphonic acid method, respectively the sulphanilic acid and α-naphtylamine hydrochlorate method, in 5076 well water samples taken twice a year out of three representative wells in every village. The prevalence of the digestive cancers (esophagus, gastric, colon, rectum, liver and pancreas) was calculated using medical records from each village during 10 years (2000–2010).

**Results:** In 3864 water samples (76.2%) nitrates level was higher than maximum acceptable level (MAL). Only 8 villages (8.5% from the entire number of the village) had an average nitrates concentration respecting MAL. In 10 years we noticed a decreasing evolution of nitrogenous compounds from an average of 130.29 mg/dm³ (95% CI = 116.22–144.35) in 2000 to 58.1 mg/dm³ (95% CI = 51.78–64.43) in 2010. Gastric cancer had the highest incidence with 1634 patients (38.06%), out of total number of 4293 digestive cancers diagnosed in rural population followed by rectum, colon, liver, pancreas and esophagus cancer. We did not find any statistical significant difference between the prevalence of cancer in villages with normal nitrates concentrations or with high nitrates concentrations. Also, we did not observed any significant difference between cancer prevalence in 2000 (when we registered the highest nitrates concentrations) or 2009 (when we registered the lowest nitrates concentrations).

**Discussion/Conclusion** In our study we did not find any relationship between cancer incidence and well water nitrates level. The potentially carcinogen aggression of nitrogenous and nitroso compounds could have been masked by feeding behavioral types which are almost the same in rural and urban communities.
Prevalence of Barrett’s esophagus in obese with GERD

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Gastroesophageal reflux disease (GERD) is common in obese patients and this is important to know because GERD may increase morbidity and mortality through its association with esophageal carcinoma. The prevalence of Barrett's esophagus (BE) in patients with GERD varies from 5% to 15%, but the relationship between BE and obesity is still unclear.

Introduction: The aim of our study was to evaluate the prevalence of BE in obese with GERD compared with normal weight patients with GERD.

Methods: We included 263 patients with GERD, 138 obese (40 males; group A) and 125 with normal weight (37 males; group B), mean age was similar in both groups, without diabetes mellitus or obesity due to endocrine disease, non-smoking. In all patients we measured BMI, waist circumference (WC), C-reactive protein and leptin and all of them underwent upper endoscopy. The diagnosis of BE was based by presence of intestinal metaplasia in biopsy specimens.

Results: BMI in obese group was 33.84 ± 7.23, and in group B was 23.32 ± 1.25, WC was 99 ± 5 cm in group A and 79 ± 5 cm in group B. BE was diagnosed in 22 patients (15.94%) in group A and in 7 patients in group B (5.6%). BE correlated statistical significant with WC but not with BMI in group A, also CRP and leptin level were significantly higher in Barrett's subgroup patients from group A. In group B, the presence of BE correlated, also with WC but not with BMI. In this group we have noticed 21 patients with normal weight but large WC. In group B leptin and CRP level were higher than normal in 42 patients but without relationship with BE.

Discussion/Conclusion: In our study BE is not a frequent disease in normal weight population with GERD, but in obese with GERD we found a high prevalence. In both groups BE correlated with WC but not with BMI. Leptin and C-reactive protein correlated with BE only in obese group.
The reliability of celiac disease serology to reflect intestinal damage

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Methods: In view of the increasing importance of the serological biomarkers for the screening and diagnosis of celiac disease, their differential performance, and the lack of head to head comparison, the reliability of those isolated or combined antibodies to reflect the intestinal damage in children with CD was evaluated.

Results: 95 pediatric CD patients (mean age 8.3), 45 nonspecific abdominal pain children (AP) (mean age 7.3), 99 normal children (NC) (mean age 8.5) and 79 normal adults (NA) (mean age 28) were tested by the following ELISAs, detecting IgA, IgG or both, IgA and IgG: AESKULISA® Gliadin (AGA), AESKULISA® tTg (tTG; RUO), AESKULISA® DGP (DGP) and AESKULISA® tTg New Generation (Neo-epitope tTg complexed to gliadin = tTg-neo). The results were compared to the degree of intestinal injury, using revised Marsh criteria. Scatter diagrams and regression analysis comparing the 12 antibodies' optical density (OD) activities to the degree of the intestinal damage were correlated.

Most of the assays were able to differentiate patients with low and high degree of intestinal damage. Comparing the different correlations between CD associated IgA and IgG antibodies' isotypes, the tTg neo IgA ($r^2 = 0.968, p < 0.0025$) and tTg-neo/DGP IgGs ($r^2 = 0.989, p < 0.0001$/$r^2 = 0.985, p < 0.0001$, respectively) stood out, significantly, as the best indicators of the intestinal damage in CD.

The highest OD values (medium 2.94 ± 1.2, $p < 0.0001$) were achieved by using the tTg-neo IgA ELISA in patients with Marsh 3c.

Discussion/Conclusion: It is suggested that tTg-neo IgA/IgG antibodies should be preferably used to reflect intestinal damage during screening, diagnosing and monitoring compliance in childhood CD.
Non-alcoholic steatohepatitis in elderly patients

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In elderly patients with non-alcoholic steatohepatitis (NASH) comorbidities and clinical characteristics were studied.

**Introduction:** The interest in non-alcoholic fatty liver disease (NAFLD) has risen due to its high prevalence in elderly patients.

**Methods:** A cohort of 47 patients aged 65.5 ± 2.7 years were examined with first time diagnosis of NASH were examined. Exclusion criteria were high alcohol and viral hepatitis. NASH was diagnosed based on clinical data (pain in subcostal area and dyspepsia), biochemical data (AST and ALT elevation ≥ 2 norm; alkaline phosphatase elevation ≥ 1.5 norm and a 2–4 fold GGT elevation) and imaging analyses (ultrasonography, fibroscan).

**Results:** Several comorbidities were found in all NASH patients: hypertension (systolic blood pressure of 170.3 ± 15.3 and diastolic blood pressure of 100.5 ± 4.5 mmHg), visceral obesity (BMI 30.1 ± 2.7 kg/m², waist circumference in females of 90.2 ± 5.3 cm and 97.6 ± 4.6 cm in males), abnormal lipid metabolism (triglycerides 1.8 ± 0.5 mol/l, total cholesterol 6.0 ± 0.08 mol/l and high-density lipoproteins 1.2 ± 0.1 mol/l). Further, all patients had hyperinsulinemia as well as high coefficient of insulin-resistance: basal insulin and the index of insulin-resistance were decreased 2 and 2.5 times, respectively. Impaired fasting glucose (IFG) was found in 35% of patients and impaired glucose tolerance (IGT) in 16% of patients. NASH treatment includes dietary recommendations with daily calorie intake restriction, hepatoprotectors (Ursofalk®), antihypertensives, cholesterol sequestrants (Ursofalk® and Mucofalk®), and in addition metformin (1500 mg/d) for correction of insulin resistance to insulin. The combined therapy had positive effects on clinical, laboratory and imaging parameters.

**Discussion/Conclusions:** NASH in elderly patients is part of the metabolic syndrome, including visceral obesity and hypertension, insulin-resistance and, in some cases, early impairment of carbohydrate metabolism (IFG and IGT), requiring a combined treatment strategy.
Hirschprung’s disease mimicking ileocolonic Crohn’s disease: A case report

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Some conditions (such as intestinal tuberculosis, metastatic cancer etc.) mimick Crohn’s disease in adults. Hirschsprung's disease (congenital aganglionosis) is the most common cause of lower intestinal obstruction in childhood. Hirschsprung’s disease is diagnosed most commonly during infancy and childhood, some cases are seen in adults. In the literature to date one case has been described with Hirschsprung's disease actually mimicking Crohn’s disease.

Case report: A 22 year-old female with a past story of constipation and abdominal pain was admitted to hospital with abdominal pain, vomiting and weight loss. She had a history of using 5-aminosalicylate and budesonide from six months of age to diagnosis of ileocolonic Crohn’s disease. Laboratory findings were WBC: 12.000/mm³, Hb: 10.6 gr/dl, Htc: 35%, plt: 352.000/mm³, ESR: 38/h, CRP: 1 mg/ml. Liver and kidney tests were normal. Colonoscopy was performed and 5–15 mm ulcers were observed in terminal ileum, transvers colon and sigmoid colon. Normal mucosal and submucosal vascular pattern was observed in the rest of colon. MR enterography imaging showed inflammation at terminal ileum and colon. During the time of the investigations she underwent to surgery due to ileus symptoms. İleocolectomy was performed. After surgery, histopathological examination was consistent with aganglionic pancolonic Hirschprung disease. She is clinically well in the following two years.

Conclusion: We describe the first case of a young female who mimicking ileocolonic Crohn’s disease and underwent surgery due to intestinal obstruction and in whom aganglionic pancolonic Hirschprung’s disease was diagnosed.
Eosinophilic oesophagitis: Presentation, diagnosis and response to therapy in a tertiary referral centre in London

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Introduction: Eosinophilic oesophagitis (EoE) is a chronic disorder characterised by an increased eosinophil infiltrate combined with symptoms of dysphagia/food bolus obstruction (FBO); This study captures recent trends in endoscopy, histology and response to therapy in patients with EoE.

Methods: Between February 2013 and January 2015, demographics, clinical characteristics and endoscopy reports were collected for all patients who were found to have > 15 eosinophils/high power field (eos/hpf). Clinical response to therapy was assessed. Mann-Whitney and Kruskal-Wallis tests were used to analyse nonparametric variables and Cox regression for multivariate analysis.

Results: 621 patients who had endoscopy presented with symptoms of dysphagia. Of the 438 (70.5%) patients that had biopsies, 43 (9.8%) had > 15 eos/hpf, 18 (42%) of whom presented also with FBO. Another 9 had refractory reflux. 29/52 (56%) exhibited EoE-specific endoscopic findings.

There was no difference in the mean eos/hpf between patients with EoE-specific endoscopic changes, oesophagitis and normal endoscopy (p = 0.299). The mean eos/hpf of those that presented with FBO (n = 16; 54 ± 23) was higher than dysphagia (n = 22; 37 ± 19) or refractory-reflux (n = 8; 43 ± 19) (p = 0.06).

Diagnosis of EoE was significantly associated with younger age (p < 0.0001), male gender (p = 0.003), pathognomonic endoscopic findings (p < 0.0001) and higher number of biopsies taken (p = 0.016).

Of the 29 patients whose outcomes after treatment were reported, all but two responded to steroids and 15 to PPI alone. A higher eos/hpf was associated with poor response to PPI (mean eos/hpf 58 ± 18 vs. 33 ± 16, p = 0.004).

Discussion/Conclusion: It is increasingly recognised that EoE does not only present with dysphagia/FBO but also with refractory reflux. Choice of therapy can be guided by the density of eosinophils, as PPIs seem to provide a reduced response in higher eos/hpf cases.
Efficacy of faecal diversion in managing refractory perianal or colonic Crohn’s disease

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Introduction: Perianal Crohn’s disease (pCD) is frequently refractory to treatment and intriguing to management. Faecal diversion with a formation of stoma has been suggested as a way to induce clinical remission in refractory patients. However, rates of restoration of intestinal continuity have been variable and relapse/need for re-operation is not uncommon. The aim of this study was to assess response and successful reversal in patients with refractory perianal and colonic CD that had a defunctioning stoma.

Methods: Between January 2005 and February 2015 92 patients with Crohn’s disease had a defunctioning stoma formation. Patients that had a temporary diversion post colectomy or due to a surgical complication and those with predominantly small bowel disease were excluded from the study. 35 patients were defunctioned for refractory perianal and 13 for colonic disease. Clinical response, successful reversal/proctectomy rates and remission at last follow up were recorded.

Results: 7/35 (20%) pCD patients had their intestinal continuity restored, out of whom 4 (57%) relapsed and needed a new stoma. Only one of the patients that were reversed stayed in clinical remission at last follow-up. 12/35 (33%) patients needed a proctectomy due to refractory symptoms. There was no significant difference in rates of stoma reversal between patients with perianal versus colonic (4/13; 31%) disease (p = 0.43). Use of biologic treatment before or after faecal diversion was not associated with higher rate of reversal (p = 0.18). Moreover, the majority of patients (pCD 73%; colonic CD 70%) had been exposed to targeted therapy prior to defunctioning operation.

Discussion/Conclusion: Faecal diversion does not seem to be a long-term effective treatment for refractory perianal or colonic Crohn’s disease. Rates of successful reversal or proctectomy are not differentiated in the biologics era.
Is there a relationship between gluten ingestion and postural tachycardia syndrome?

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Introduction: Postural tachycardia syndrome (PoTS) is a group of disorders of autonomic dysfunction, characterised by orthostatic intolerance (OI). Gastrointestinal disturbance including abdominal pain and bloating is also commonly reported. Despite symptom overlap with the gluten-related disorders, the relationship between coeliac disease (CD), gluten sensitivity (GS) and PoTS has not been previously evaluated. We aimed to determine the prevalence of self-reported GS and CD in a cohort of patients with PoTS.

Methods: One hundred patients with PoTS were recruited from the syncope clinic to complete a validated questionnaire which screened for GS. Case notes were reviewed to determine the outcomes of relevant GI investigations. Patients on a gluten-free diet (GFD) ranked on a Likert scale the severity of abdominal pain and OI before and after starting the GFD.

Results: The self-reported prevalence of GS was 42% (42/100; 94% female; median age 27 years). 27% (27/100) of patients were on a GFD. 4% (4/100) of the cohort had biopsy-proven CD (3 female; median age 24 years). This was higher than the local population prevalence of CD (0.8%; OR 4.9, 95% CI 1.3–18.8, p = 0.02) [1]. Patients felt their abdominal pain had improved since starting a GFD (median score 8 to 4, respectively; p = 0.0001), but no change in symptoms of OI (p = 0.084).

Conclusion: There is a high prevalence of self-reported GS in this group. The data also suggests that CD may be more common in PoTS than the general population, but further studies with appropriately matched controls are required to ascertain the nature of this relationship.

Reference:

Analysis of several candidate genes role in acute pancreatitis

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Introduction: The hereditary nature of pancreatitis is widely discussed but until recent time only one gene (PRSS1 – encoding cationic trypsinogen) is accepted responsible for pancreatitis. Taking into account the multimodal nature of acute pancreatitis (AP) we hypothesized that more genes may be responsible for its different pathogenetic aspects determining the clinical picture, treatment response and outcome.

Methods: Ninety-eight AP patients (39.80% women, 60.2% men, mean age 48.52 ± 6.09, 44.88% alcoholic AP, 56.12% biliary AP) participated in the study. 120 healthy volunteers formed control. PRSS1 – encoding cationic trypsinogen gene R122H polymorphism, CFTR – the cystic fibrosis transmembrane conductance regulator protein gene F508C polymorphism and IL-4 gene C-590T polymorphism attracted our attention as they regulate major links of AP pathogenesis (trypsinogen activation, pancreatic excretion and inflammation). All gene studied in PCR.

Results: Despite its role in promoting trypsinogen activation there was no difference between study and control group allele distribution of PRSS1 gene. Moreover, no difference was observed between alcoholic AP and biliary AP groups. C-allele of CFTR gene was significantly more frequent in study group compared to control; only 15.3% were heterozygous. 58.16% of study group patients had T-allele of IL-4 gene compared to 45.0% in control (p < 0.01). There was minor but statistically significant (p < 0.05) difference between alcoholic AP (61.36%) and biliary AP (54.55%) groups in T-allele distribution. TT-carriers had generally heavier course of disease compared to heterozygous and CC-carriers.

Discussion/Conclusion: Our study presented somehow confusing results with no clinically significant evidence of PRSS1 gene R122H polymorphism. This may be explained by the fact that both study and control groups consisted of adult individuals while PRSS1 gene usually determines AP onset much earlier (10–20 yrs). C-allele of CFTR gene independently on aetiology and T-allele of IL-4 gene depending on AP' aetiology are significant independent risk factors for AP and its severity.
Kefir supplement and chronic constipation

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Introduction: Kefir is a probiotic fermented milk product. Our goal was to evaluate the effects of kefir on the symptoms and colonic transit of patients with chronic constipation.

Methods: Twenty-two consecutive patients with functional constipation according to the Rome III criteria were divided into two groups: 1. The slow transit group (GROUP1) (n = 11) for which 500 mL/day of a probiotic kefir beverage was administered for 4 weeks; and 2. The slow transit group (GROUP2) (n = 11) without Kefir administration. Defecation parameters (stool frequency, stool consistency, laxative consumption) were recorded in diaries daily by the patients.

Results: At the end of the study, the patients in GROUP1 showed an increased stool frequency (p < 0.002), improved stool consistency (p = 0.028), and decreased laxative consumption (p = 0.039). No significant statistical differences were found in GROUP2.

Discussion/Conclusion: This study shows that kefir has positive effects on the symptoms of constipation and accelerates colonic transit.
Effect of a high-fat diet in gallstones formation process

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Introduction: Diet appears to play an important role in cholelithiasis. Biliary cholesterol is transported mainly by vesicles and micelles. The first stage in the formation of gallstones corresponds to biliary cholesterol crystallization, derived from unstable vesicular transporters.

The aim of this study was to investigate the influence of consuming a high-fat diet on serum lipids, and assess their implications in gallstones formation.

Methods: The experimental design was quantitative, and we settled for two groups of BALB/c mice: one control (n = 10), and the other (n = 10) treated with a high-fat diet (43% neutral fat and 0.13% cholesterol). After 2 months, the animals were sacrificed, and blood and bile samples were obtained. We determined serum glucose and the corresponding lipid profiles. In bile samples, cholesterol and phospholipids levels were analyzed, and cholesterol transporters (vesicles and micelles) were separated by gel filtration chromatography.

Results: Treated animals showed: 1) increase by 50% in serum total cholesterol (control: 99 ± 10 mg/dL vs. treated: 148 ± 10 mg/dL; p < 0.05); 2) increase of 97% in HDL-cholesterol (control: 38 ± 11 mg/dL vs. treated: 75 ± 10 mg/dL; p < 0.05); 3) no change in LDL-cholesterol; 4) no variation in serum triglycerides; 5) no change in glycemia; 6) no change in biliary lipids (cholesterol: 4.1 ± 0.3 mM and phospholipids: 33.5 ± 0.6 mM); 7) increase of vesicular transporters in bile (control: 2.9 mM vs. treatment: 7.6 mM); 8) no variation in micellar transporters (control: 30.5 mM vs. treatment: 28.2 mM).

Discussion/Conclusion: A high-fat diet significantly increase total cholesterol and HDL-cholesterol, without changing LDL-cholesterol, triglycerides and glycemia. Even though we did not see changes in the total bile lipids, an increase in vesicular transporters of cholesterol in the treated group was observed. We conclude that a diet high in fat may contribute to the formation of gallstones in our experimental model.
Treatment of induced colitis in mice by the Ras antagonist farnesylthiosalicylic acid (FTS)

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Background and Aims: Ras proteins have been shown to regulate cell growth, proliferation, differentiation. Targeting the Ras family has been suggested as a therapeutic strategy in proliferative and inflammatory diseases. Farnesylthiosalicylic acid (FTS) is a synthetic Ras antagonist that inhibits the binding of Ras to discrete membrane sites, thereby down-regulating several Ras-dependent signaling functions and accelerating Ras degradation. This study examines the role of Ras in the inflammatory process of colitis, and examines whether the Ras antagonist FTS can prevent it.

Methods: Colitis was induced in 26 Balb/c, 8–10 weeks old, female mice by adding 5% dextran sodium sulfate (DSS) to their drinking water and allowing them to drink ad libitum for 7 days. Twelve mice were treated with FTS (5 mg/kg) 3 times a week, and 14 mice were treated with 0.9% normal saline. After 7 days the mice were sacrificed and the colon was isolated for further evaluation. Colonic damage was assessed clinically by using a disease activity score which combines weight loss and rectal bleeding, and histologically by evaluating colonic segments stained with haemotoxylin and eosin. Mucosal myeloperoxidase activity, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) levels were measured by ELISA. The expression of Ras and Ras downstream effectors such as P-ERK was determined by immunobloting assays.

Results: Mice treated with FTS had a significant lower disease activity score ($P = 0.0001$), and a lower histopathologic score (NS). A significant reduction was found in the inflammatory response in the FTS treated mice expressed by myeloperoxidase activity ($P = 0.007$), the levels of TNF-α ($P = 0.04$) and the levels of IL-1β ($P = 0.01$). The expression of Ras was found to be lower in the group treated with FTS ($P = 0.004$), opposing to the expression of P-ERK which was found to be higher in that group ($P = 0.003$).

Conclusions: Ras inhibition significantly ameliorates the severity of experimental colitis, and may offer a new therapeutic approach.
Elevated MMP-3 levels in early RA patients after Borrelia infection

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Introduction: To investigate the influence of infectious disease on rheumatoid arthritis (RA), patients were screened for Borrelia. Sera from 204 RA patients in an early state of the disease < 6 months, were tested for Borrelia antibodies, cyclic citrullinated peptides (CCP), rheumatoid factors (Rf) and MMP-3. Sera from follow up visits of some of those patients were tested.

Methods: Sera were screened by ELISA The quantitative determination of human IgA, IgG and IgM rheumatoid factors was performed with the AESKULISA® Rf-AGM, CCP titres checked with the AESKULISA® CCP-IgG and -IgM, Borrelia antibodies with the AESKULISA® Borrelia-IgG and -IgM and levels of MMP3 with the AESKULISA® DF MMP-3.

Results: 10.8% tested at their 1st visit were positive for Borrelia-specific antibodies. 18/204 patients were positive for IgG or IgM, or both, and 4/204 patients were equivocal. Borrelia-positive sera showed completely negative results in the classical RA parameters Rf-AGM and CCP. 5/22 Borrelia-positive patients were positive for CCP but negative for Rf-AGM. Interestingly, 10/13 patients which were negative for classical RA parameters had high MMP-3 levels (> 120 ng/ml), while only 1/9 of CCP-positive patients showed elevated titres of MMP-3. Interestingly, classical RA parameters remained negative in 3 patients until their 4th follow up visit. Only 1 patient was positive for CCP testing throughout the investigated time period.

Discussion/Conclusion: Not only Borrelia inflammatory responses, but also periodontitis, an inflammatory disorder of the mouth, and RA share common pathogenic mechanisms. The co-measurement of MMP3 may assist in improved differential diagnosis, whilst at the same time helping to eliminate unnecessary patient therapies, thus saving time, money and improving overall patient care. Further studies have to be done to investigate the role of MMP-3 testing for early RA diagnosis and the role of Borrelia infection in the development of RA.
Effects of calcium pyruvate in the DCA experimental model of irritable bowel syndrome

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Introduction: Since disappointing results are frequently obtained with the available pharmacological treatments for IBS, new drugs are demanded for these patients. In this study we evaluated the effects of calcium pyruvate (CaPyr) in an experimental model of IBS in rats induced by intracolonic administration of deoxycholic acid (DCA).

Methods: Male Sprague Dawley rats (240–320 g) were administered DCA once daily on 3 consecutive days, and then divided into the different experimental groups (n = 8): three received orally and daily CaPyr (40 and 100 mg/kg) or Gabapentin (70 mg/kg); a non IBS and an untreated control IBS group were also included. One and two weeks after, abdominal withdrawal reflex to colorectal distension (CRD) was semi-quantitatively scored. Also the referred pain was evaluated with von Frey filaments. After two weeks of treatment, all rats were sacrificed and the expression of different markers evaluated in the colonic tissue by qPCR: IL-1β, COX-2, the mucins MUC-2 and MUC-3, the receptors for serotonin HTR-4 and the toll like receptor TLR-3.

Results: After one or two weeks of treatment, the treated groups showed reduced CRD scores values than IBS control. Also, the referred pain was attenuated in those groups treated with CaPyr and gabapentin. The IBS process was associated with altered expression of the different markers studied and the treatments were associated with a restoration in the expression of IL-1β and COX-2, as well as that of TLR-3. The decreased expression of the mucins were only upregulated with CaPyr, whereas only gabapentin was able to ameliorate the expression HTR-4.

Discussion/Conclusion: CaPyr was able to exert beneficial effects in the experimental model of IBS, with a similar efficacy to that showed by the standard therapy Gabapentin and this effect was associated with an improvement of the altered immune response clearly involved in IBS.
Intestinal anti-inflammatory effects of goat whey in the DNBS model of mouse colitis

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Introduction: The whey is a byproduct of cheese that contains important nutritional components including oligosaccharides. These have been considered as prebiotics, which can exert beneficial effects in intestinal inflammation. In the present study, the intestinal anti-inflammatory effect of goat whey was tested in the experimental model of colitis induced by 2,4-dinitrobenzenesulfonic acid (DNBS) in mice.

Methods: Male CD1 mice were assigned to four groups: non-colitic, control colitic and colitic groups treated with goat whey (4 g/kg/day) for 12 days before DNBS colitis induction and continuing until the sacrifice, which took place 4 days later. Then, the colon was analyzed macroscopically, and tissue explants were obtained to determine the secretion of some pro-inflammatory mediators by ELISA. Besides, analysis of gene expression in colon samples was performed by RT-qPCR.

Results: Weight loss was more significant in control colitic group than in the treated groups, being more relevant in those mice receiving pasture-fed goat whey. Macroscopically, administration of goat whey to DNBS-colitic mice resulted in an intestinal anti-inflammatory effect as evidenced by a reduction in the weight/length ratio compared with non-treated colitic mice. Treatment with the goat whey reduced the colonic expression of some of the mediators involved in the inflammatory response, such as pro-inflammatory cytokines (TNFα, IL-1β and IL-6), the chemokine MCP-1, the adhesion molecule ICAM-1, as well as the enzymes iNOS and MMP-9. Treatments were also able to significantly up-regulate the expression of markers of epithelial integrity such as MUC-3 and ZO-1, thus revealing an improvement in the altered colonic permeability that characterizes colonic inflammation.

Discussion/Conclusion: The goat whey showed beneficial effects in the DNBS colitis model in mice, which could be related to a down-regulation of the immune response and to the improvement of the intestinal epithelial barrier function.
**Intestinal anti-inflammatory activity of probiotics in DNBS-colitis: Impact of role micro-RNA expression and gut microbiota**

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**Introduction:** Probiotics have been reported to be useful in IBD treatment through different mechanisms, including their immunomodulatory properties and the impact in the microbiota composition. These effects can promote the down-regulation of inflammation mediators including micro-RNAs. The aim was to evaluate the immunomodulatory properties of different probiotics in DNBS model of mice colitis, emphasizing the relation between micro-RNA expression and bacterial diversity.

**Methods:** Male CD1 mice were pretreated with *E. coli* Nissle 1917 and *L. fermentum* CECT5716 at 5 x 10⁸ UFC/mice/day for 20 days before DNBS-induced colitis (3 mg/mouse). Non-colitic and non-treated colitic groups were included as reference. Four days after colitis induction, mice were sacrificed. The inflammatory status was evaluated by body weight, colonic weight/length, qPCR of inflammatory markers and micro-RNAs, and changes induced in microbiota populations characterized by pyrosequencing. Different ecological parameters of biodiversity were evaluated. Statistical significance is set at p < 0.05

**Results:** The administration of probiotics resulted in an intestinal anti-inflammatory effects evidenced biochemically by a decreased expression of pro-inflammatory cytokines (IL-1β, TNF-α) and an increased expression in mucins (MUC-2) and occludines. Also, it was established a micro-RNA expression profile which showed a reduced expression of miR-143, miR-375 and miR-150 while miR-155 and miR-223 were increased in this model. Probiotics were able to restore the expression of these markers. Finally, dysbiosis and lowering bacterial diversity was characterized in colitic mice by 454-pyrosequencing, being restored by the treatment with each probiotic. The biodiversity was modified in colitic group and restore by the treatments.

**Discussion/Conclusion:** Probiotics are able to increase the diversity of microbiota as well as to alter the expression of different inflammatory markers and micro-RNAs. These results support the immuno-modulatory effects of probiotics and its use in IBD.
Impact of \textit{Nlrp3} x gut microbiota interactions on experimental colitis and insulin sensitivity

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Introduction: NOD-like receptor pyrin domain containing 3 (\textit{Nlrp3}) genotype has been shown to affect murine experimental colitis and glucose metabolism. We here investigate whether \textit{Nlrp3} genotype-induced changes in gut microbiota composition are involved in the observed effects.

Methods: Female \textit{Nlrp3}\textsuperscript{-/-} and wild-type (WT) littermates underwent dextran sodium sulphate (DSS)-induced acute (7 days, 1\% DSS) or chronic colitis (4 x 7 days, 1\% DSS). Colitis severity was evaluated by body weight change, colonoscopy, mRNA expression of pro-inflammatory cytokines and histology. Male \textit{Nlrp3}\textsuperscript{-/-} and WT littermates received a high fat diet (HFD) or normal chow for 6 weeks and glucose tolerance was assessed. Gut microbiota composition was studied by 16S rRNA amplicon sequencing before and after induction of colitis/HFD. Additionally, samples of the Swiss IBD cohort (SIBDC) from patients with \textit{NLRP3} polymorphisms will be analyzed to compare and extend the relevance of our findings to human gut microbiome x genotype interactions.

Results: \textit{Nlrp3}\textsuperscript{-/-} mice showed a more severe phenotype in acute and chronic DSS colitis. HFD-fed \textit{Nlrp3}\textsuperscript{-/-} mice showed slightly improved glucose tolerance compared to WT littermates. Notably, \textit{Nlrp3}\textsuperscript{-/-} and corresponding WT littermates differed strongly in their gut microbiota composition under basal conditions as well as after induction of colitis.

Discussion/Conclusion: Gut microbiota composition, experimental colitis and glucose tolerance are affected by the \textit{Nlrp3}\textsuperscript{-/-} genotype. Further experiments with microbiota transfer between genotypes, and colitis models/HFD experiments in animals with a limited defined flora will address a causal relationship between gut microbiota composition and colitis/glucose tolerance outcome. By analysis of the gut microbiota functionality using PICRUSt and by profiling of host tissue at mRNA and metabolite level we aim to gain detailed insight into the microbiota x host interactions and their role in the pathology of inflammatory bowel disease and insulin resistance.
Yellow fever vaccination during treatment with infliximab in a patient with ulcerative colitis: A case report

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Introduction: For the first time we report the case of a 59 years old patient who accidentally underwent live vaccination against yellow fever during continuous treatment with the TNF-α-AB infliximab for ulcerative colitis, a chronic inflammatory bowel disease (IBD).

Methods: A search of the literature using PubMed (search terms: anti-TNF, infliximab, yellow fever vaccination) resulted in 14 publications.

Results: Case report: The clinical course showed fever of short duration and elevation of liver enzymes without further clinical complications. Yellow fever viremia was not detectable.

Discussion/Conclusion: A primary vaccination against yellow fever under infliximab has not been reported in the literature before, although vaccination is an important topic in IBD. Live vaccinations, like stamaril against yellow fever, are contraindicated during TNF-α-AB treatment. Treatment regimens containing TNF-α-AB are of growing importance, not only in gastroenterology, but also in rheumatology and dermatology. We discuss this topic by presenting our case and reviewing the current literature.
Titanium dioxide nanoparticles promote intestinal inflammation through activation of the inflammasome

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#equal contribution

Introduction: Western life style and diet are major environmental factors playing a role in the development of inflammatory bowel disease (IBD). Titanium dioxide (TiO2) nanoparticles are widely used as food additives or in pharmaceutical formulations and are consumed by millions of people on a daily basis. We investigated the effects of TiO2 in the development of colitis and the role of the nucleotide-binding oligomerization domain receptor, pyrin domain containing (NLRP)3 inflammasome.

Methods: Wild type and NLRP3-deficient mice with dextran sodium sulfate-induced colitis were orally administered with TiO2 nanoparticles. The pro-inflammatory effects of TiO2 particles in cultured human intestinal epithelial cells (IECs) and macrophages were also studied, as well as the ability of TiO2 crystals to traverse IECs monolayers and accumulate in the blood of IBD patients using inductively coupled plasma mass spectrometry.

Results: Oral administration of TiO2 nanoparticles worsened acute colitis through a mechanism involving the NLRP3 inflammasome. Importantly, crystals were found to accumulate in spleen of TiO2 administered mice. In vitro, TiO2 particles were taken up by intestinal IECs and macrophages, and triggered caspase-1 cleavage, caspase-1-NLRP3 assembly, and the release of NLRP3-associated interleukin (IL)-1β or IL-18. TiO2 also induced reactive oxygen species generation and increased epithelial permeability in IEC monolayers. Increased levels of titanium were found in blood of ulcerative colitis patients with active disease.

Discussion/Conclusion: These findings indicate that individuals with a defective intestinal barrier function and preexisting inflammatory condition, such as IBD might be negatively impacted by the use of TiO2 nanoparticles.
Descriptive analysis of 320 consecutive patients with non-variceal acute upper gastrointestinal bleeding

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Introduction: The aim of study was to investigate trends in a tertiary hospital admissions for acute non-variceal upper GI bleeding (NVUGIB) and to identify the factors associated with a higher mortality rate in Iasi, Romania.

Methods: In this prospective, descriptive analysis, we have studied data of consecutive patients with NVUGIB confirmed by upper digestive endoscopy (performed in Institute of Gastroenterology and Hepatology, Iasi), patients that were admitted in Gastroenterology and Surgery Departments of "St. Spiridon" Emergency Hospital during one year period (2014).

Results: A total of 320 patients with confirmed NVUGIB were admitted: M/F 69.6%/30.4%, mean age 55.5 ± 9.12 years (40.9%, n = 131 between 60–79 years, and 12.5%, n = 40 over 80 years). The most common symptoms of NVUGIB were melaena (n = 165, 51.56%), haematemesis (n = 138, 43.12%) or syncope (n = 16, 5.0%). Overall, 9.3% (n = 30) of patients were hemodynamically unstable (BP < 100/60 mmHg) and 26.25% (n = 84) of patients had severe anemia (Hb < 7 g/dl). The endoscopic sources underlying NVUGIB were: gastric ulcers (n = 115, 35.9%), duodenal ulcers (n = 103, 32.18%), Mallory-Weiss syndromes (n = 42, 13.1%), and gastric tumors (n = 13, 4%). The Forrest class stratification was: Ia 3.8%, Ib 19.7%, IIa 12.9%, IIb 36.2%, IIc 8.2%, III 19.2%.

Among our study group, 33 patients (10.3%) had history of UGIB and one of the most important bleeding risk factor was consumption of non-steroidal anti-inflammatory drugs, anti-platelets and anticoagulants (n = 51, 15.9%, p = 0.003), followed by alcohol (n = 24, 7.5%, p = 0.006). Recurrent bleeding was observed in 7.3%. The mortality rate within 30 days from bleeding episode was 7%.

Discussion/Conclusion: Gastric ulcer is the most common cause of NVUGIB. Despite progress in NVUGIB management, the group of patients who had bleeding recurrency or surgical indication was associated with significant morbidity and mortality rates.
Upper gastrointestinal bleeding: Non-variceal vs. variceal haemorrhage

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

Methods: We evaluated 637 patients admitted in Institute of Gastroenterology and Hepatology, St. Spiridon Emergency Hospital, Iasi for AUGIB between 1st January 2012 and 31st October 2012. Demographic characteristics, haemodynamic parameters on admission, endoscopic features, blood analyses were done and were prospectively monitoring during the hospitalization time. A comparison between AUGIB from esophageal varices and non-variceal causes was made, regarding mortality rate, number of hospitalization days and number of blood transfusions needed.

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

Discussion/Conclusion: Non-variceal bleeding is the most common cause of acute upper gastrointestinal bleeding. In hospital mortality, rate of rebleeding, average hospitalization days and need of blood transfusions are higher in patients with variceal haemorrhage.
Role of SMAD7 in the intestinal epithelium for gut homeostasis

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Since polymorphisms in the SMAD7 gene have been associated with an increased risk for developing colorectal cancer, we want to investigate the role of SMAD7 in the intestinal epithelium for gut homeostasis and development of intestinal cancer using mice with an intestinal epithelial cell specific deletion of SMAD7 to study the molecular mechanisms influenced by SMAD7.

Introduction: TGF-β signaling controls a diverse set of cellular. The main regulatory mechanism of the TGF-β signaling pathway is mediated by its inhibitor Smad7. Recent data showed the involvement of Smad7 in different diseases as patients with inflammatory bowel disease, for example, show increased Smad7 expression in the mucosa. In the present study, we investigate the role of Smad7 in intestinal homeostasis.

Methods: Animals with floxed Smad7 allele in intestine epithelial cells (IEC) flanked with Cre-recognition sequences were crossed with mice expressing Cre-recombinase under control of the villin promoter. Mice were sacrificed and small intestine as well as colon were collected for histology, morphometry and immunohistochemistry.

Results: Histological and morphometric evaluations revealed no differences in epithelial structure of small and large intestine of Smad7⁰⁻ or Smad7ΔIEC mice as well as the analysis of differentiated intestinal cell types and immune cells. A reduction of proliferation was present in Smad7ΔIEC in comparison to control animals shown by stainings of the proliferation marker Ki-67 and on mRNA-expression levels.

Discussion/Conclusion: In conclusion, these data show that the knock-out of Smad7 in mice has no influence of the appearance on the intestinal epithelium. On the other hand Smad7ΔIEC mice showed a reduced proliferation. As it is known that Smad7 plays also an important role in the development of colon cancer it is of great interest to understand the underlying molecular mechanism.
Endoscopic and morphological characteristics of the upper gastrointestinal tract mucosa in young males with dyspepsia

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Introduction: The verification of gastric dyspepsia cause is frequent clinical problem and very important for determining of treatment. We aimed to determine the underlying causes of dyspepsia in young males.

Methods: 235 young males (18–27 years) with symptoms of dyspepsia who underwent esophagogastroduodenoscopy at the City Medical Center were included in this single-center study. Morphological analysis of their biopsies was made. We use criteria of dyspepsia defined the Rome III Committee.

Results: Lesions of upper gastrointestinal tract at endoscopy were found in 102 cases (43.4%; 95% CI: 38.3–48.5). Ulcer and/or postulcer deformity with/without erosive changes were found in 28 patients (11.9%; 95% CI: 5.8–15.6), including 8 cases of acute duodenal ulcer. On the other hand 30 patients had erosive changes of gastroduodenal area without ulcer and/or postulcer deformity. In our study 13 patients (5.4%; 95% CI: 3.2–9.1) had esophagitis various grade, including 12 cases in a combination with erosive-ulcerous lesions of gastroduodenal area. Among 133 patients without erosive-ulcerous lesions in 131 cases the signs of chronic gastritis were found at morphological examination of biopsies. Gastropathy and duodenopathy were diagnosed in 102 from them at endoscopy. Prevalence of the contamination Helicobacter pylori (HP) of gastric mucosa is summarized in table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>HP contamination</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>All patients with dyspepsia</td>
<td>235</td>
<td>126</td>
</tr>
<tr>
<td>Gastric ulcer and duodenal ulcer</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Erosive changes of gastroduodenal area</td>
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<td>18</td>
</tr>
<tr>
<td>Gastropathy/duodenopathy + macroscopic normal</td>
<td>133</td>
<td>68</td>
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<tr>
<td>Gastritis</td>
<td>131</td>
<td>68</td>
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Discussion/Conclusion: Among young males (18–27 years) the most common cause of dyspepsia is gastritis. In 58 cases were found erosive-ulcerous abnormalities. Prevalence of the contamination HP of gastric mucosa was high in this group.
Assessment of pancreatic exocrine function and fat-soluble vitamins during an episode of acute pancreatitis

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Introduction: It is known that pancreatic exocrine insufficiency (PEI) has been reported after acute pancreatitis (AP) regardless its severity in about 12% of patients and leads to nutritional deficiency especially for fat-soluble vitamins A, D, E. However, pancreatic function could be restored. Our aim was to determine PEI distribution and to assess main markers of malnutrition (fat-soluble vitamins) that could be used for PEI monitoring.

Methods: Study encompassed 40 patients (20 male), mean aged 49 years, who consented to participate; 17 patients suffered from recurrent chronic pancreatitis and 23 from first episode of AP. Alcohol abuse was most common etiology (31 patients). AP severity was assessed by Revised Atlanta criteria (mild, moderate, severe). PEI was determined by fecal elastase-1 (FE-1) test (ScheBo Biotech AG). Fat-soluble vitamins A, E, D were assessed by HPLS and LC-MS/MS methods. Statistical analysis was performed via SPSS vs.19.

Results: Mean FE-1 levels for all patients was 307 µg/g feces. 13 patients (34%) had PEI (FE-1 < 200 µg/g feces) of which 46% were with severe insufficiency (FE-1 < 100 µg/g feces). Mild, moderate and severe AP were present in 32%, 42% and 26%, respectively. There was not statistically significant difference between FE-1 levels in different severity groups (p > 0.05), but the difference between patients with single episode AP and more than two episodes AP was significant, p < 0.05. FE-1 was not significantly related to sex, age or etiology. Deficiency of vitamin A (< 200 µg/L), E (< 5 µg/L) and D (< 75 nmol/L) were determined in 2%, 82% and 89%, respectively. Fat-soluble vitamin status worsened with severity of AP which was demonstrated in differences of means values for vitamins A and D.

Discussion/Conclusion: Routine FE-1 evaluation during episode of AP is useful both for starting early and accurate dosed pancreatic enzyme replacement therapy and for assessing the exocrine function and nutritional panel follow-up requirement.
Treatment optimization of the long-term non-scarring gastro-duodenal ulcers

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Despite the use of modern treatment standards of gastroduodenal ulcers (GDU), it is not always possible to achieve clinical and endoscopic remission of peptic ulcer (PU), associated with H. pylori (HP). One of the effective ways to improve medical complexes in patients with PU and long-term non-scarring gastroduodenal ulcers (life threatening situations) is the use of the 2 (1H)-quinolone – rebamipide.

The aim was to study the rebamipide effectiveness in combination with eradication therapy in PU pts associated with HP.

The study involved 56 patients with HP-positive PU, torpid disease course, who were divided into 2 groups depending on the treatment complexes administration: I (n = 26) group – the eradication therapy ( pantoprazole, clarithromycin, amoxicillin) 14 days, II (n = 30) – rebamipide 300 mg/day for 28 days in addition to the eradication therapy.

Mucus-producing function of mucous barrier of stomach (MBS) was evaluated by content of N-acetylneuraminic acid (NANA) and fucose in the blood serum and by their excretion with urine.

Clinical and endoscopic PU remission in 28 days was recorded in 24 (92.3%) patients of group I and 30 (100%) patients of group II, while HP eradication in 22 (84.6%) patients of group I and 28 (93.3%) patients of group II.

After the therapy had been completed the NANA concentration in group I reduced in 1.15 times, group II in 1.3 times (p < 0.001). NANA excretion with urine in group I decreased in 1.1 time, group II in 1.3 times (p < 0.05). Due to the anti-HP-therapy and rebamipide the NANA excretion with urine was in 1.2 times (p < 0.05) lower that in group. The blood serum concentration of fucose bound with proteins in group I patients increased in 1.6 times (p < 0.001). The similar changes were detected when studying fucose excretion with urine.

In patients of group II the normalization of initially reduced parameters was noted – the level of B-lymphocytes, the IgG, IgA increased.

The administration of rebamipide in combination with anti-HP-therapy increases the therapeutic effectiveness by enhancing duodenal mucous barrier resistance in patients with the long-term non-scarring ulcers.
Gastric involvement and Helicobacter pylori in Kaposi’s sarcoma

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Introduction: Kaposi’s sarcoma (KS) is usually presented as skin lesions. Since the gastrointestinal tract is rarely involved in KS patients, endoscopists are not familiar with gastric lesions. In the present study, we aimed to evaluate patients with classical KS and Acquired Immuno-Deficiency Syndrome (AIDS)-associated KS with respect to gastric symptoms, gastric involvement and presence of Helicobacter pylori (H. pylori).

Methods: This study included 18 patients with KS. Forty patients, admitted to outpatient clinic for H. pylori, were included as control group. Stage of the disease, therapy, dermatological and oral examination findings were recorded. All patients were asked about gastric symptoms and underwent upper gastrointestinal (GI) endoscopy. Biopsies were taken from areas suspected as KS involvement and from corpus and antrum for the presence of H. pylori, and results were compared with control group.

Results: Among the 18 patients included in the study, 17 (94.4%) of them were male and the mean age of the patients were 59.3 (39–79). Fifteen patients had classical KS (83.3%) while 3 had (16.7%) AIDS-associated KS. Of the 5 patients suspected of having KS on upper GI endoscopy, the diagnosis of KS were verified in 3 patients histopathologically. Fundus and corpus was involved in 2 patients and antrum was involved in 1 patient. None of the biopsies taken from areas other than gastric lesions had any findings associated with KS. In general, 10 patients (55.6%) were symptomatic. Two of 3 (66.6%) patients with gastric involvement and 8 of 15 (55.3%) patients without gastric involvement were symptomatic. H. pylori was positive in 66.6% of all patients with KS and in 52.5% of patients in the control group (p = 0.206). Two patients with KS and gastric involvement were positive for H. pylori, and these patients had oral involvement as well as AIDS-associated KS, and were younger.

Discussion/Conclusion: Presence of gastric symptoms were not enough to doubt about gastric involvement in KS patients. Gastric involvement is more frequent in patients with oral involvement and in those with AIDS-associated KS. There is no difference between patients with and without KS in terms of H. pylori positivity.
An IBD-associated variant in PTPN22 protects from disease onset in mouse models of colitis

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Introduction: Presence of the single nucleotide polymorphism (SNP) rs2476601 in the gene locus encoding protein tyrosine phosphatase non-receptor-type 22 (PTPN22) results a gain-of-function PTPN22 protein and is associated with increased risk to develop autoimmune disorders, but reduces the risk for Crohn’s disease (CD) onset. Here we addressed how presence of the gain-of-function variant in PTPN22 influences the susceptibility to intestinal inflammation in mouse models of colitis.

Methods: Colitis was induced in 10–12 week old female mice by administration of 2% DSS for 7 days (acute DSS colitis), administration of four cycles of DSS (1.5% DSS for 7 days, followed by 10 days normal drinking water; chronic DSS colitis), or by transferring naïve T cells into RAG2−/− recipients. Wild-type (WT), PTPN22 deficient (PTPN22−/−), or mice expressing the IBD associated gain-of-function variant in PTPN22 (PTPN22-619W mice) were used for the study.

Results: While PTPN22−/− mice suffered from aggravated acute DSS colitis, PTPN22-619W mice reacted only weak to the DSS treatment when compared to WT littermates. In chronic DSS colitis however, PTPN22−/− showed more pronounced colitis. In the T cell transfer model, PTPN22−/− T cells induced more severe colitis, while mice transfected with PTPN22-619W T cells were protected from disease development in the first weeks, and later developed only a mild disease.

Discussion/Conclusion: During acute inflammation, loss of PTPN22 results in enhanced colitis severity, while presence of the gain-of-function PTPN22 variant protects from colitis development. In chronic disease, compensatory mechanisms reverse the increased disease-susceptibility in PTPN22−/− mice, finally resulting in reduced disease severity, while presence of the gain-of-function variant can no longer protect from colitis. We here describe for the first time how the IBD-associated variant in PTPN22 affects colitis development what helps to explain why this variant is associated with a reduced risk for CD onset.
High resolution manometry profile of hiatal hernia in patients before and after fundoplication

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Introduction: High resolution manometry (HRM) accuracy in diagnosing hiatal hernia (HH) is lacking. This study was aimed to compare HRM variables in patients with HH before and after fundoplication as well as to evaluate sliding HH.

Methods: Sensitivity and specificity of HRM were assessed in 31 patients with gastroesophageal reflux disease who were qualified for Nissen fundoplication and underwent preoperative HRM. Intraoperative diagnosis of HH was the gold standard. Area under curve (AUC) of receiver operating characteristic (ROC) reflected diagnostic accuracy of HRM. Eleven patients out of 31 were selected who underwent both: HRM before fundoplication and at least 3 months after surgery. Manometric protocol included 10 consecutive swallows of 10 ml of water. Data analysis was done with esophageal pressure topography according to the Chicago Classification.

Results: 29 patients out of 31 were found to have sliding HH during surgery while 14 patients had manometric criteria for HH. In HRM there were no false positive results although 15 false negative results were shown. Sensitivity and specificity of HRM in detecting HH were 48% and 100% respectively. AUC under ROC curve for HRM was 0.74 indicating limited usefulness of this method (0.8 is the threshold). HRM profile of HH in preoperative group is characterised by significantly lower p < 0.01 median minimal basal esophagogastric junction (EGJ) pressure: 0.5 mmHg (-2.8, 4.1) as well as integrated relaxation pressure (IRP) 1.5 mmHg (-0.7, 3.7) comparing to postoperative group without HH 6.5 (4.6, 14.8) and 5.2 (2.1, 11.8) respectively. IRP values were within normal range in both examined groups (< 15 mmHg). Neither DCI nor IBP was affected by fundoplication.

Discussion/Conclusion: HRM is not reliable tool to diagnose sliding HH. Surgical correction of HH contributes to higher EGJ relaxation pressure and improvement of antireflux barrier however neither bolus pressurization nor DCI is affected by fundoplication.
High resolution manometry profile in patients before and after fundoplication

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Introduction: The aim of the study is assessing lower esophago-gastric junction and esophageal peristalsis by high resolution manometry (HRM) in patients with gastroesophageal reflux disease (GERD) before and after laparoscopic Nissen fundoplication.

Methods: HRM was performed in 25 patients with GERD before fundoplication (preoperative group) and at least 3 months after surgery (postoperative group). Manometric protocol included 10 swallows of 10 ml of water. Data analysis was done with esophageal pressure topography according to the Chicago Classification.

Results: In the postoperative group the median basal LES pressure: 15.8 mmHg (15.2–23.7) as well as the minimal basal LES pressure: 7.3 mmHg (4.6–13.9) was significantly higher than in the preoperative group: 10.0 (5.7–15.6; p < 0.05) and 7.3 (4.6–13.9; p < 0.001) respectively. Median integrated relaxation pressure (IRP) was also significantly higher (p < 0.001) in the postoperative group: 6.0 mmHg (2.9–11.4) as compared with the preoperative group: 2.0 (0–3.3). Before fundoplication 11 patients had hiatal hernia, but no after surgery. It was found significant increase of intrabolus pressure (IBP): 13.9 mmHg (11.7–20.8) and decrease of contractile front velocity (CFV): 2.9 cm/s (2.0–4.0) in the postoperative group as compared with preoperative group: 2.9 (2.0–4.0; p < 0.05) and 4.3 (3.1–5.4; p < 0.01) respectively. Distal contractile integral (DCI) was significantly higher in postoperative group, however, based on DCI threshold (450 mmHg/s/cm) it was only trend from ineffective to effective esophageal motility (p = 0.07). Double-peaked waves were more frequent p < 0.01 in the postoperative (0–78%) than in preoperative group (0–22). Early dysphagia was observed in 8 of 25 patients after fundoplication.

Discussion/Conclusion: HRM is valuable tool related to LES characteristic of GERD patients before and after fundoplication. Fundoplication establishes antireflux barrier by increasing LES pressure and correcting hiatal hernia. Even moderate increased of IRP may contribute to motility disorders and pressurization in some patients after fundoplication.
Short-term vitamin D supplementation improves hepatic steatosis as quantified by controlled attenuation parameter (CAP)

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries. A recent meta-analysis has confirmed decreased serum 25-hydroxyvitamin D levels in patients with NAFLD. This intervention study investigates whether vitamin D therapy ameliorates hepatic steatosis in patients referred to the outpatient liver clinic of a tertiary centre.

Methods: We prospectively recruited 40 patients with NAFLD and vitamin D deficiency, as defined by serum concentrations < 20 ng/ml. Hepatic steatosis was assessed using the controlled attenuation parameter (CAP), which quantifies the degree of ultrasound attenuation by liver fat during vibration-controlled transient elastography (FibroScan). Patients were included if they had significant liver fat accumulation, which was defined by a CAP ≥ 280 dB/m. Serum 25-hydroxyvitamin D was measured by chemiluminescent immunoassay and body composition with bioelectrical impedance analysis. Patients received 20,000 IU vitamin D daily for 7 days, thereon weekly for 6 months, while vitamin D, liver function tests, BMI and CAP levels were monitored.

Results: Overall, the cohort comprised 47.5% women (mean age 54.9 ± 12.1 years; mean BMI 29.5 ± 3.0 kg/m²). Moderate vitamin D deficiency was present in 57.5% and severe vitamin D deficiency (< 10 ng/ml) in 42.5% of patients. Fatty liver quantification showed a mean CAP of 329.8 ± 31.6 dB/m. The CAP score was higher in patients with severe vitamin D deficiency (339.4 ± 31.6 vs. 322.7 ± 30.4 dB/m). CAP scores significantly decreased by 5% at the 4-week interval (310.8 vs. 329.8 dB/m, P = 0.012). During this short time period, a rapid increase in vitamin D levels was noted (31.6 vs. 10.9 ng/ml, P < 0.0001), however, LFTs, BMI and body fat levels remained unchanged. Patients will be monitored again at 3 and 6 months.

Discussion/Conclusion: Vitamin D levels correlate with the degree of hepatic steatosis, which significantly improves after only 4 weeks of vitamin D replacement therapy. We conclude that hepatic steatosis as assessed by CAP is a dynamic process, which appears to be modulated by short-term therapeutic interventions such as vitamin D substitution. The molecular mechanisms underlying hepatocellular lipid remodelling by vitamin D remain to be identified.
Biliary reflux syndrome as a cholecystectomy complication: An underevaluated disease

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Introduction: Biliary reflux (BR) syndrome or duodenal gastroesophageal reflux is comparatively rare state in healthy subjects (if isolated) and is difficult to differentiate from gastroesophageal reflux disease. It complicates chronic gastric ulcer, cholecystitis, gastroduodenitis, and several surgeries, including gastric resections, gastroenterostomies and cholecystectomies. The aim of the study is to clarify the frequency, clinical signs, and treatment options for BR after cholecystectomies.

Methods: The study is based on the results of surgical treatment of 132 patients with cholelithiasis. Ninety-one of them (75.0%) postoperatively presented complaints of bitter taste in the mouth, infrequent vomiting, and regurgitation, retrosternal pain. Majority were female (113, 85.61%), the age of patients varied from 29 to 71 years. All patients underwent endoscopies (with biopsies if necessary), gastric and esophageal pH, X-ray.

Results: Among 132 patients 99 (75.0%) had BR. 33.33% of them had bitter taste in the mouth permanently, in other cases patients complained for recurring bitterness. Retrosternal pain occurred in 53.54% of patients and in only two cases (2.02%) its occurrence could be associated with cardiac pathology. Regurgitations observed in 27.27% of patients. Gastric pH above 5.0 was observed in all patients, in 79.80% of case the number of reflux episodes varied between 3 to 5. X-ray examination showed delayed gastric and duodenal evacuation in 33.33% of cases, duodenogastral reflux detected in all patients. Disorders of lower esophageal sphincter, its insufficiency, gastroesophageal reflux, chest pain, esophageal antiperistaltic, regurgitation, and dysphagia were detected in 92.93% of patients. Treatment included ursodeoxycholic acid 500 mg; modified silica based sorbent, proton pump inhibitors and gastric mucosa protective drugs. Sucralfate was used when morphological changes were found endoscopically and domperidone to stimulate normal peristalsis. Therapy was effective in 63.64% after 4 weeks and in 81.82% after 3 months of treatment.

Discussion/Conclusion: BR syndrome is much more frequent than expected analysing literature sources. Endoscopy and X-ray exam are the most potent diagnostic measures for BR. Adequate treatment may significantly improve BR symptoms and increase patients' quality of life.
"Hepatic view" on acute pancreatitis

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Introduction: Acute pancreatitis (AP) causes primary disabilities in 10.9–15.0% patients with digestive system pathologies. Three organ systems are generally recommended to be assessed to define organ failure in AP: respiratory, cardiovascular and renal, focusing on systemic multiple organ failure syndrome. However, hepatic dysfunction is to great extent under evaluated while common pathogenetic mechanisms put liver into even further danger under condition of acute pancreatitis. We hypothesized that even mild to moderate AP significantly influences hepatobiliary system.

Methods: Study included 86 patients with moderate (oedematous) AP: 35 (40.7%) female, 51 (59.3%) male, mean age 48.6 ± 6.12; 44.18% patients with alcoholic AP, 55.81% with biliary AP. Liver and pancreatic functions were studied by their enzymatic activity. In addition, plasma levels of total cholesterol (TC), triglycerides (TG), low density, and high-density level cholesterol (LDL-C, HDL-C) were evaluated. Obtained data analyzed in Statistica 7.0 software.

Results: Patients with alcoholic AP had reduced liver detoxication function with prevalence of cytolytic (AST, ALT) and AST/ALT ratio increased 2–2.2 times, p < 0.05 and cholestatic pathogenetic mechanisms (increased γ-glutamyl transpeptidase by 1.7–2.7 times, p < 0.05). System of intraacinar pancreatic enzymes presented signs of stimulation (trypsin increased by 3.4–6.5 times, p < 0.05) and protease inhibitors activation (alpha-1 antitrypsin elevation by 10.7% (p < 0.05), with low serum elastase activity. Acute biliary pancreatitis is accompanied by expressed systemic inflammatory response: C-reactive protein serum level increased 15.4–34.7 times (p < 0.001) mostly due to biliary AP group (difference between biliary and alcoholic AP – 2.25 times, p = 0.027). Alpha-1 antitrypsin elevated by 17.3% (p < 0.05); essential dyslipidaemia (HDL-C decrease and LDL-C increase) was observed with no reliable differences in pancreatic enzymes aggressiveness comparatively to alcoholic AP (p > 0.05).

Discussion/Conclusion: The course of interstitial (oedematous) AP is accompanied by deregulation of lipid metabolism, in-creased indicators of systemic inflammatory response and reliable changes in the content of organ-specific enzymes.
Molecular-genetic predictor for colonic dysbiosis formation in patients with mesenteric vessels endothelial dysfunction

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Introduction: Various digestive diseases and vascular-endothelial injury has to some extend common pathogenesis realized through metabolic and immune mechanisms involving vascular and digestive systems injury. However, both may have strong molecular-genetic background. There is no clear data emphasizing genetics, vascular-endothelial changes and colonic dysbiosis. The aim of this study is to evaluate the endothelial function and mesenteric vessels remodelling depending on A1166C polymorphism of angiotensin II type 1 receptor (AGTR1) gene in patients with colonic dysbiosis and vascular-endothelial injury as well as determine the dysbiosis in these patients.

Methods: Study included 104 patients with colonic dysbiosis (CD) combined with arterial hypertension – AH (50 female, 54 male, age 53.2 ± 8.7). Intimae-media thickness (IMT) of abdominal aorta (AO) and other flow mediated parameters of mesenteric vessels state evaluated by sonography. NO (nitrite/nitrate) plasma concentration, vascular adhesive molecule (sVCAM-1) level was defined by IEA. AGTR1 (A1166C) genes polymorphisms assessed with PCR.

Results: In patients with moderate and complicated AH microbial overgrowth syndrome II–IV degree detected in 95.1–95.9% of cases, significantly more (p < 0.001) than in moderate AH patients (64.3%). CC AGTR1 gene genotype carriers had heavy dysbiosis of III–IV grades. Patients with A-allele, had lower frequency of dysbiosis (p = 0.004) and moderate severity (p = 0.037). CC genotype of AGTR1 gene characterized by elimination of obligate colonic indigenous constant microorganisms and contamination by pathogenic (E. coli Hly+) and opportunistic (Proteus), Enterobacteriaceae, Peptococci, Clostridium and Candida fungi. In patients with CC genotype of the AGTR1 gene a significant reduction of Bifidobacteria (35.7%, p < 0.001), Lactobacilli (24.1%, p < 0.01) and enterococci (1.5%) was found. On this background, significant increase of enterotopathogenic Escherichiae (8.94 ± 0.08 lg CFU/g), opportunistic Enterobacteriaceae (8.78 ± 0.11 lg CFU/g ), Hafniae (8.69 ± 0.09 lg CFU/g), Proteus – by 55.2%, Staphylococci (5.92 ± 0.14 lg CFU/g), Candida fungi (5.60 ± 0.10 lg CFU/g) was observed.

Discussion/Conclusion: The CC genotype of AGTR1 gene is accompanied by elimination of normal colonic autochthonous obligate microflora and contamination by pathogenic and conditionally pathogenic microorganisms. The mechanism involves changes of mesenteric arteries and endothelial function.
The lack of pH-sensing receptor TDAG8 plays a protective role in murine adoptive transfer colitis model

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

Methods: Naïve T-cells (CD4+CD62L+) from WT and TDAG8/-/- donor mice were injected into Rag/-/- mice and typical markers of colitis were investigated after 8 weeks.

Results: The WT group showed severe weight loss (p = 0.013). The KO group exhibited only a minor delay in weight gain as compared to untreated animals. No significant difference was observed in colon length, spleen weight or colonoscopy score. Nevertheless, there was a trend towards less severity in the colonoscopy score of the TDAG8/-/- group. In addition, the KO group displayed a lower histopathology score of colitis as compared to the control group. Furthermore, reduced RNA expression of pro-inflammatory cytokines (INF-γ, TNF, IL17a, IL18) was observed in the KO group.

Discussion/Conclusion: In a murine adoptive transfer colitis model we demonstrated that transfer of TDAG8-deficient naïve T-cells caused less severe colitis as compared to WT cells. Our data indicate that the pH-sensing receptor TDAG8 plays a protective role in mucosal immunology.
Health quality and sexual dysfunction in Turkish IBD patients

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**Background:** In inflammatory bowel disease (IBD) patients, there is an impaired quality of life (QoL) and sexual dysfunction. However, there might be some differences between countries because of different cultures and socio-economical alterations. In this study, we aimed to evaluate the frequency of sexual dysfunction and the level of QoL in Turkish IBD patients.

**Methods:** In this study, we evaluated 112 IBD patients (64 patients with ulcerative colitis: 57%) and 42 control subjects. All patients and control subjects were asked to fill three questionnaires (SF 36, Hospital Anxiety and Depression Scales [HAD-A and HAD-D], Arizona Sexual Experience Scale [ASEX]). Demographic characteristics are collected and disease activity was determined for each patient.

**Results:** In all evaluated patients, demographic data (age, disease activity, gender, education) was not different from each other. Inpatient subjects had more severe disease than outpatient subjects as expected. Smokers and ex-smokers were more frequent in Crohn's disease group whereas there were no difference in alcohol consumption. HAD-D scores were significantly higher in both ulcerative colitis (UC) and Crohn's disease (CD) patients when compared to control group. However, there was no difference between two disease groups. HAD-A scores were significantly higher in CD group when compared to UC and control subjects. There was no difference between UC and control group. Female patients had more anxiety scores, there were no correlation between depression scores and gender. Both HAD-D and HAD-A scores are positively correlated with educational status. When SF-36 scores were evaluated, in both disease groups, scores were worse than control group as expected, whereas there was no difference between UC and CD patients. Sexual dysfunction frequency was different between three groups, however, patients with more severe disease had more sexual dysfunction. Conclusions

In conclusion, we found no difference between CD/UC groups and control group for sexual dysfunction scores. However, with the increase in disease activity, both UC and CD patients have more sexual dysfunction than control subjects. Disease activity was also found to be positively correlated by anxiety and depression score whereas, there was a negative correlation between disease activity and QoL. Anxiety and depression were seen more frequently in highly educated subgroup.
Lactobacillus bulgaricus GLB44 and Helicobacter pylori infection – A possible eradication: Preliminary clinical results

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Introduction: Lactobacillus delbrueckii subsp. bulgaricus has in vitro inhibitory properties against Helicobacter pylori [1]. The effect of Lactobacillus bulgaricus GLB44 in commercially available form on H. pylori infection was evaluated in clinical practice.

Methods: Twenty four patients (50% female) at mean age 45.46 ± 13.3 years were enrolled in our study after esophagogastrroduodenoscopy. All patients were Helicobacter pylori (HP)-positive diagnosed either by rapid urease test, stool antigen test and histology examination, or by a combination of these methods. Every patient was given Lactobacillus bulgaricus GLB44 (capsules and tablets) in daily doses of 15 x 10⁹ living cells together with rabeprazol 20 mg bid for 7 days, followed by GLB44 alone for 3 days at the same dose. Control stool immunochromatographic antigen tests were performed in all patients after at least 43 days.

Results: After the course of treatment 91.7% of the previously HP-positive patients had negative control stool antigen tests. There were two patients still positive for HP (8.3%) and they both had unsuccessful antimicrobial eradication courses in the past.

Discussion/Conclusion: Per oral route of administration of adequate probiotic dose in combination with PPI is a promising treatment modality in HP positive patients.

Reference:

Modification of inflammatory microRNAs in gastric mucosa by aspirin, NSAIDs and proton-pump inhibitors

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Background: Gastric carcinogenesis is a multistep *H. pylori*-related process. MicroRNA alteration is a crucial contributing event in the progression from chronic inflammation to gastric cancer.

Aim: To evaluate the potential of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and PPI on molecular modification of mucosal inflammatory microRNAs (miRNAs) miR-155 and miR-223 in *H. pylori* (Hp) infected and non-infected subjects.

Material and Methods: The study was performed in two cohorts: 1) interventional study in 20 healthy subjects with and without *H. pylori* infection (each n = 10), and 2) in prospective case-control observational study (n = 188). In interventional settings, low-dose aspirin (100 mg) was given for 7 days and upper GI-endoscopy including histological sample collection was accessed on the days 0, 1, 3, 7. Nine *H. pylori* eradicated subjects repeated the protocol following eradication treatment. Patients from the second cohort underwent upper GI endoscopy including histological evaluation, *H. pylori*-testing (incl. cultivation), biopsy collection and systematic questioner to NSAIDs and PPI use. MiR-155 and miR-223 were evaluated in total RNA from the biopsies using TaqMan Assay and subsequently correlated with COX-2 expression level.

Results: miR-155 and miR-223 expression is strongly dependent on *H. pylori*-infection in gastric mucosa and in short-term view shows a trend for reversal following eradication treatment. Daily low-dose aspirin as well as NSAIDs intake did not influence the expression both in healthy subjects and in patients. However, regular PPI intake was associated with a substantial reduction of miR-155 expression predominantly in antral mucosa of patients with CG independently from density of neutrophils and mononuclear infiltrate. Furthermore, miR-155 expression showed an inverse correlation to COX-2 levels in subjects without *H. pylori*-infection.

Conclusions: PPI but not NSAIDs or low-dose aspirin are associated with changes in expression of mucosal inflammatory miRNAs in *H. pylori* dependent manner.
Intestinal anti-inflammatory effect of olive leaf extract in the DSS model of mouse colitis

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Introduction: Extracts from olive (Olea europea) leaves are used in Mediterranean traditional medicine as an anti-inflammatory remedy. They contain antioxidant phenolic compounds, like oleuropeoside, which could be interesting for the treatment of inflammatory conditions associated with oxidative stress in humans, including inflammatory bowel disease. The aim of the study was to evaluate the intestinal anti-inflammatory properties of an olive leaf extract in the dextran sodium sulfate (DSS) model of mouse colitis, which resembles human IBD.

Methods: Male C57BL/6J mice were assigned into five groups: non-colitic, colitic control and colitic treated groups with olive leaf extract (0.1-0.5-1 mg/kg) from the day of colitis induction (3% DSS in the drinking water for 5 days) until one week after the establishment of the colitic process. The inflammatory status was evaluated macroscopically by a disease activity index (DAI), and biochemically by colonic determination of mediators of inflammation and intestinal epithelial barrier function. In vitro immunomodulatory properties of the extract (0.1-100 mg/ml) were determined in LPS-stimulated cell lines.

Results: According to the DAI values, the treatment improved the recovery of the colitic mice, maybe through a reduction of the colonic expression of pro-inflammatory mediators (IL-1β, IL-6, TNFα, ICAM-1 and MIP-2), and significantly up-regulating key players of the intestinal epithelial integrity (occludin, ZO-1 and MUC-3). Besides, it displayed immunomodulatory properties in vitro since it inhibited LPS-induced nitrite production in RAW cells and decreased IL-6 production in LPS-stimulated CMT-93 cells.

Discussion/Conclusion: The olive leaf extract showed intestinal anti-inflammatory activity in the DSS model of mouse colitis, maybe be related to its antioxidant properties as well as the downregulation of the immune response. The extract could also improve the intestinal epithelial barrier and also have a direct effect on immune cells, as demonstrated in the in vitro studies.
A comparison of outcomes of endoscopic retrograde cholangiopancreatography versus percutaneous transhepatic biliary drainage in the management of obstructive jaundice from hepatobiliary tuberculosis: The Philippine General Hospital experience

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Significance: This study aimed to determine the prevalence of hepatobiliary tuberculosis (HBTB) with biliary obstruction and to compare the outcomes of endoscopic retrograde cholangiopancreatography (ERCP) versus percutaneous transhepatic biliary drainage (PTBD) in these patients.

Methodology: This is a cross-sectional study involving patients from Philippine General Hospital (PGH) who underwent biliary drainage from HBTB from January 2009 to June 2014. HBTB was defined as having evidence of TB (culture, smear, PCR, histology) or clinical diagnosis with the triad of jaundice, fever and calcifications on imaging with other causes of jaundice excluded. The primary outcome was successful drainage and secondary outcomes were mean hospital stay and complications. Simple logistic regression was used to identify factors associated with success of drainage, z-test for two proportions to compare outcomes of ERCP versus PTBD and t-test to compare mean hospital stay post-procedure.

Results: There were 441 patients who underwent ERCP and PTBD, 19 fulfilled the inclusion criteria. 11 underwent ERCP while 8 had PTBD. There were more successful cases in PTBD versus ERCP but this was not statistically significant (p value 0.3615). Factors such as age, gender, location and nature of obstruction, vices, coexisting pulmonary or other extrapulmonary TB and presence of portal hypertension did not affect success rates in these patients. The PTBD group had longer mean hospital stay but this was not significant (p value 0.1880). There were no complications reported in both groups.

Conclusion: HBTB comprises 4.3% of the patients undergoing biliary drainage in PGH. Both ERCP and PTBD are equally safe and effective in the management of biliary obstruction from HBTB.

Keywords: cross-sectional, hepatobiliary tuberculosis, obstructive jaundice, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic biliary drainage
Developments of novel diagnostic findings on capsule endoscopy in the small bowel of patients with Crohn’s disease

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Introduction: Definitive diagnosis for Crohn's disease (CD) at an early stage can optimize treatment strategy and can improve prognosis. However, thus far, no specific diagnostic criteria have been established based on the small bowel (SB) findings on capsule endoscopy (CE). In the present study, we aimed to identify and confirm the novel findings using CE in the SB of patients with CD.

Methods: We investigated the derivation cohort study and subsequently performed a prospective randomized study. The derivation cohort included 90 cases (cases with established ileitis or ileocolitis CD [n = 52], suspected CD [n = 8], intestinal Behçet’s disease [n = 5], and infectious enteritis [n = 5], and users of non-steroid anti-inflammatory drug [NSAIDs; n = 13] and aspirin [n = 7]). Thereafter, we conducted a prospective randomized controlled study to confirm the specific CE findings (UMIN000008199). Three investigators were trained to observe specific findings from among the CE videos; these investigators were then blinded to the clinical backgrounds of patients included in the prospective randomized study, and assessed the CE videos of the patients.

Results: In the derivation cohort, the specific CE findings were determined for 51 CD cases (85.0%). These novel findings included the transition from aphthae to erosion, as well as to small or longitudinal ulcers, as the capsule endoscope progressed towards the distal portion of the SB. These transition of the small bowel lesion (TSL) in patients with CD was observed significantly more frequently in patients with CD than in patients with other diseases (1 of 30 cases, 3.3%: P < 0.01). Our prospective randomized controlled study included 20 patients with established ileitis or ileocolitis CD and 20 patients with long-term NSAIDs or aspirin users (11 NSAIDs, 5 aspirin, and 4 both; the control group). All 40 patients were tested for functional patency of the gastrointestinal tract using a patency capsule, of which 14 were confirmed in each group. TSL was accurately diagnosed in 12 of 14 CD patients (85.7%) and was accurately diagnosed in 1 in 14 NSAIDs or aspirin users (7.1%; P = 0.02); the difference in the diagnostic accuracy rate was statistically significant. TSL was provided high availability (specificity 85.7%, sensitivity 92.9%, positive predictive value 92.3%, and negative predictive value 86.7%).

Discussion/Conclusion: TSL is a novel CE finding in SB lesions in CD patients. TSL can be used in the differential diagnosis between CD and other inflammatory bowel diseases in patients with limited distribution of such lesions in the SB during the early stages. Early diagnosis and appropriate optimized treatment may improve prognosis in patients with CD of the SB.
Methotrexate use for maintenance therapy in pediatric Crohn’s disease

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Introduction: Methotrexate (MTX) is recommended in the current guidelines (ECCO, ESPGHAN, DGVS) as an option for maintenance therapy in children with Crohn’s disease (CD) either primary or in thiopurine failure. MTX was neglected by many pediatric gastroenterologists in the past but is increasingly used currently. This retrospective study investigated safety and efficacy of MTX in children and adolescents with CD.

Methods: All children with CD ever treated with MTX at our hospital from 2007 to 2015 were included. Treatment modalities, duration of MTX therapy, time of steroid-free remission, Pediatric Crohn’s Disease Activity Index (PCDAI), concomitant therapy with TNF-blockers and adverse events were recorded.

Results: Twenty-three patients (12 boys, 52%) with a mean age at diagnosis of 10 years (± 3.5 SD, range 3–16) and a mean disease duration of 31 month (± 29 SD, range 0–127) received MTX, predominantly subcutaneously. Mean dosage was 15 mg (± 3.8 SD, range 12–25) and mean observational time was 20 month (± 16.1 SD, range 3–66). Folic acid was given to all 48 hours after MTX. All except two patients had azathioprine prior to MTX. In three patients azathioprine was discontinued due to pancreatitis, in the others due to lack of response. Eight patients had been steroid-dependent.

Mean PCDAI at start of MTX was 41 points (± 11 SD, range 10–55). After three month mean PCDAI dropped to 24 points (± 17 SD), after six month to 20 points, and after twelve month to 15 points (± 10.5 SD, range 5–38). After nine months steroid-free remission (PCDAI < 15) was achieved in about half of the patients. Twelve patients (52%) needed additional anti-TNF therapy during observational period and seven patients discontinued MTX. Most commonly reported adverse events have been nausea in 21% (never leading to discontinuation), transaminase elevation in 14% (leading to discontinuation of MTX therapy in one patient) and loss of hair in 14% (well responding to dose reduction in all).

Conclusion: MTX can be effective and is well tolerated in CD patients. The most important side effect is hepatotoxicity, which can be easily detected by monitoring. Effective contraception is absolutely essential by both men and women receiving MTX. We will continue in following-up our patients, but more and also controlled studies are needed to identify patients who are likely to respond to MTX.
Interferon-λ signalling drives multi-organ disease during bacterial infections

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Introduction: Recent studies demonstrated that type III interferons (IFN-λs) are an important part of host immune responses to viral infections and moreover IFN-λ treatment is currently evaluated as a potential therapeutic option in chronic virus-induced hepatitis. However, the role of these novel cytokines in bacterial induced diseases remains to be fully elucidated. Here we investigated the role of IFN-λ dependent immune-responses in bacterial infections.

Methods: A novel BAC-transgenic dual-reporter IFN-λ2/λ3 mouse strain, mice deficient in IFN-λ signal transduction and mice that systemically overexpress IFN-λ were analyzed in experimental models of gut microbiota induced polymicrobial sepsis and gram negative septic shock.

Results: Initially, we analyzed IFN-λ expression in mice systemically subjected to the intestinal microbiota. As a result qPCR/ELISA analysis demonstrated a strong upregulation of IFN-λ expression in serum/organs that depended on the presence of TLR4 and the IRF3 transcriptional activator. Furthermore, analysis of IFN-λ2/λ3 dual reporter mice by luciferase and β-galactosidase assays identified infection-dependent promoter activity in several organs systems including livers, lungs and kidneys. Interestingly, mice deficient in IFN-λ signaling, subjected to cecal-ligation-and-puncture (CLP) showed significantly increased survival compared to controls. Survival post CLP model was associated with highly decreased systemic spread of infection, inflammatory responses and organ injury. Similar results were obtained in a model of LPS induced septic-shock, where high apoptosis in IFN-λ receptor expressing epithelial cells in the gut and other organs was observed. In line with these observations, a transgenic-overexpression strategy leading to increased serum-levels of IFN-λ resulted in increased systemic bacterial loads, tissue injury and mortality in these mice.

Discussion/Conclusion: In conclusion, the present data suggest that activation of IFN-λ/IFN-λR signaling contributes significantly to bacterial sepsis and this could have implications for human disease.
Impact of adding antimicrobial agents to endoscopic retrograde cholangiography (ERC) contrast media for prevention of infectious complications in patients with biliary obstruction – A monocenter retrospective study

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Aims: The benefit of systemic antibiotic prophylaxis in ERC remains controversial. We investigated whether local application of antimicrobial agents into ERC contrast media is efficient to prevent post-ERC infectious complications in a high-risk study population.

Methods: Eighty-four ERC cases were analyzed in this retrospective case-control study. All patients suffered from biliary obstruction, most frequently due to sclerosing cholangitis (75%) and malignant stenosis (9.5%). Of these, 42 received vancomycin 500 mg, gentamicin 80 mg and fluconazole 40 mg into ERC contrast media. Microbial testing of bile fluid was performed in 35 (83.3%) patients receiving intraductal antibiotics. After ERC, all patients were followed up over 72 hours for signs and symptoms of infection. The effect of intraductal antibiotics on infectious post-ERC complications was calculated using multivariate logistic regression analysis.

Results: Post-ERC infectious complications were observed in 20 cases (23.8%). Microbial testing of bile fluid was positive in 91.4% of treated cases. 93% of the detected bacteria were sensitive to the administered antibiotics. Patients receiving antibiotics into contrast media exhibited a significantly lower post-ERC infection rate than those without intraductal antibiotics (14.3% vs. 33.3%; p = 0.04). The odds ratio (OR) for the risk of post-ERC infection in patients receiving intraductal antibiotics was 0.33 (95% confidence interval [CI]: 0.114–0.978). When analyzing for the most common risk factors of post-ERC infections (acute cholangitis and incomplete biliary drainage), the beneficial effect of intraductal antibiotic prophylaxis was even more evident (OR = 0.153; 95% CI: 0.039–0.598). Patients profiting most obviously from intraductal antibiotics were those with secondary sclerosing cholangitis.

Conclusion: Local application of a combination of antibiotic and antimycotic agents into ERC contrast media efficiently reduced post-ERC infectious complications in patients with biliary obstruction. We advocate prophylactic intraductal antimicrobial treatment especially for those patients with cholangitis prior to ERC and patients with secondary sclerosing cholangitis.
Role of cross-sectional imaging modalities in determining therapeutic options for patients with de novo stricturing Crohn’s disease

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Introduction: In patients with de novo stricturing Crohn’s disease (CD), cross-sectional imaging modalities such as abdominal ultrasonography (USG), computed tomography (CT) and magnetic resonance enterography (MRE) can provide complementary information on the characteristic features of this disease. Here we describe a patient whose clinical course shows how these imaging modalities in combination can be useful in following the inflammatory and fibrotic features of mixed ileo-colonic stricture.

Results: A 34-year-old woman presented at our inflammatory bowel disease (IBD) outpatient clinic with severe abdominal pain, nausea, weight loss and decreased frequency of bowel movements, all of which had been present for the past week. Three and a half years before this visit she had been diagnosed with ileo-colonic inflammatory CD, and for the last three years she had been taking adalimumab (ADA, 80 mg/month) and azathioprine (AZA, 125 mg/day). At the time of diagnosis, colonoscopy had shown ileo-caecal inflammation, hyperemia and erosion as well as an incomplete stricture narrowing the lumen. CT images showed ileal wall thickening (11 mm), mucosal ulcers and a narrowed lumen spanning 190 mm. Biopsy was compatible with CD, and the Crohn’s disease activity index (CDAI) was calculated to be 249. A steroid and AZA regimen was started and symptoms were relieved. The CT images, when interpreted along with colonoscopy findings and symptomatic response to immunosuppressive treatment, suggested that the stricture was inflammatory.

Seven months later, the patient experienced moderate activation (CDAI 228). Ultrasonography showed ileal wall thickening (4 mm), narrowed lumen and prestenotic dilatation. MRE revealed moderate ileal wall thickening, mucosal irregularity, edema, mucosal hyperenhancement, luminal disruption, stenosis and prestenotic dilatation. Colonoscopy showed an incomplete stricture with ulcerations, hampering the advance of the scope, suggestive of mixed inflammatory stricture. The clinical picture interpreted as AZA resistant mixed inflammatory Crohn’s disease, and ADA was added to the treatment. After 8 weeks of ADA 40 mg every two weeks the patient showed no response and the dose was increased to 40 mg per week. The patient’s symptoms improved and she remained in remission for 17 months. She then presented with the symptoms described above. Her CDAI was 264 and colonoscopy showed complete stricturing obstruction of the ileo-caecal valve. Abdominal ultrasonography showed ileo-caecal stenosis with prestenotic ileal dilatation (21 mm). These findings were also...
detected on MRE, without any ileal wall thickening, mucosal edema or hyper-enhancement, consistent with pure short segment fibrotic stricture. Endoscopic balloon dilatation was performed in an attempt to relieve the obstructing symptoms. Her symptoms subsided and ADA treatment was tapered to 40 mg twice a month. Six months later EBD was repeated because of persisting mild obstructive bowel symptoms.

**Discussion/Conclusion:** In conclusion, for patients with CD, especially those with strictureing disease, the combined use of USG, CT and MRE provides critical information for rational treatment and follow up.
A combination of PillCam®SB2 and SmartPill® in the investigation of patients referred for assessment of known or suspected small-bowel Crohn’s disease and their association with faecal calprotectin levels: Case series

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Introduction: SmartPill® (Given Imaging Corp., Yoqneam, Israel) is an ingestible, wireless, non-imaging capsule device that records physiological data including contractions, pH and temperature throughout the gastrointestinal (GI) tract [1]. There are currently scarce data looking at SmartPill® assessment of patients with known or suspected small-bowel Crohn’s disease (CD) [2]. We designed this pilot study to investigate feasibility and safety of SmartPill® assessment of gut motility in this group (local ethics committee approval ref.12/SS/0013).

Methods: Over one year (2012), patients with known or suspected CD, referred for small-bowel capsule endoscopy (SBCE), were invited to participate. Patients underwent hydrogen breath test to exclude small-bowel bacterial overgrowth, patency capsule (Agile®) to confirm luminal patency and provided stool samples for faecal calprotectin (FC). Patients ingested PillCam®SB2, then SmartPill® 4h afterwards. Thirty-three healthy controls were obtained from unpublished data. For statistical analysis, \( P < 0.05 \) was considered significant.

Results: Over the aforementioned period, 12 patients were recruited (7F/5M, mean age 44.2 ± 16.6 years). 10 underwent complete SmartPill® examination (1 stomach retention, 1 dropout). Pillcam®SB2 was complete in 10 (1 stomach retention, 1 dropout). Mean FC was 340 ± 307.7 \( \mu \)g/g. The study group had longer transit times and lower gut motility index (MI) compared to controls, where \( MI = \ln (\text{sum of pressure amplitudes x number of contractions + 1}) \). The difference in motility appears statistically significant \( (P < 0.05) \). Transit times for SmartPill® were longer than PillCam®SB2 (not statistically significant), possibly due to differences in capsule specifications. Limitations: signal loss from SmartPill® (5/10 studies), possibly due to radiofrequency interference.

Discussion/Conclusion: This study is the first pilot to attempt combining SBCE and SmartPill® in clinical assessment of small-bowel CD. Current data on motility in CD is scarce. Multimodal information could provide a clearer clinical picture [3–5]. Furthermore, despite concerns about capsule retention in CD patients, our study suggests SmartPill® appears safe for use if a patency capsule is employed beforehand.
References:


Correcting liver function in pancreatic cancer patients with obstructive jaundice

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Purpose: The purpose was to study the effect of conservative therapy on patients with pancreatic cancer with the complication of obstructive jaundice.

Material and Methods: A prospective analysis of liver function correction therapy was carried out and included 45 patients with pancreatic cancer with the complication of obstructive jaundice T3-4N0-1M0-1, who underwent decompression of the biliary tract followed by multicomponent hepatotropic and infusion therapy. Percutaneous decompression of the biliary tract was performed in 32 (71.1%) cases, and retrograde stenting with plastic prosthesis in 13 (28.9%) cases. Postoperative therapy included colloid plasma substitutes based on hydroxyethyl starch and protein emulsions with antibacterial and local hemostatic therapy. In addition to improving the rheological properties of bile and liver function, liver protectors and ursodeoxycholic acid medications were used.

Results: Relative hypovolemia and hypoproteinemia with hypercoagulation were observed on the second postoperative day. These tended to be most clearly expressed in patients with baseline bilemia > 150 mkmol/l. In addition, autolysis of hepatocytes with intracellular enzyme rates was observed to increase by a factor of more than 2.5. The average volume of allocated bile via external drainage was 317 ± 11.2 ml/day. Following multicomponent hepatotropic and infusion therapy, there was a positive trend towards the normalization of enzymatic indicators. The average volume of allocated bile increased up to 533 ± 13.2 ml/day. Analysis of bile biochemical composition and viscosity found that the bile viscosity had completely returned to normal by the tenth postoperative day, but the relative imbalance between free and bound bilirubin components was maintained (average 1:2 respectively), which indicates the presence of latent hepatic insufficiency. Thus, our analysis shows the effectiveness of multicomponent conservative therapy in patients with pancreatic cancer following biliary tract decompression. Hepatotropic therapy improves the rheological properties of bile and restores hepatocyte functional activity.
Fascin-1 as a marker of precursor lesions of pancreatic cancer

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Introduction: Fascin-1 is a globular actin cross-linking protein which is required for the formation of actin-based cell-surface protrusions that are essential for cellular migration and cell – matrix adhesion. Fascin-1 is usually absent in normal epithelial cells, but its expression is significantly upregulated in transformed epithelial cells and several types of human carcinoma, especially in pancreatic cancer. The aim of our study was to explore the role of actin-binding protein, Fascin-1 in development of pancreatic intraepithelial neoplasia.

Material and Methods: The study included 70 patients with PanIN (with different diagnosis – acute and chronic pancreatitis, pancreatic cysts, neuroendocrine tumor, pancreatic ductal adenocarcinoma) and 38 normal pancreatic tissues as a control. Fascin expression was evaluated using immunohistochemistry with the monoclonal antibody.

Results: In normal pancreatic ducts Fascin-1 expression was absent, in PanIN 1A was weak and in PanIN 1b, 2 and 3 was strong. There was a positive correlation between Fascin-1 expression with age (p = 0.034) and PanIN (p < 0.001). Higher expression of Fascin-1 was observed in people over 60 years old. Moreover, expression of this protein increased with increasing histological grade of PanIN. It was demonstrated statistically significant differences in Fascin-1 expression in normal pancreatic ducts compared with PanIN (p < 0.001). There were also statistically significant differences in Fascin-1 expression in PanIN 1 in comparison to PanIN 2 (p < 0.001) and PanIN 1 vs. PanIN 3 (p < 0.001).

Conclusions: Overexpression of Fascin-1 is correlated with increased histological grade of pancreatic intraepithelial neoplasia and occurs relatively early in the pathogenesis of PanIN. Fascin may provide a new cancer prevention strategy as a possible therapeutic molecular target to inhibit the progression of pancreatic intraepithelial neoplasia.
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Konzerthaus Freiburg
Freiburg, Germany