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SYMPOSIUM OF GASTROENTEROLOGY
REGENSBURG, GERMANY
MAY 24TH, 2019
PROGRAM AND ABSTRACTS



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**University Hospital Regensburg
Department of Internal Medicine I
Regensburg, Germany**

**6th GERMAN-ROMANIAN SYMPOSIUM OF
GASTROENTEROLOGY**

REGENSBURG, May 24th, 2019

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Scientific Committee

Prof. Dr. Martina Müller Schilling, Regensburg

Prof. Dr. Monica Acalovschi, Cluj-Napoca

Program and Abstracts

Scientific Programme

Friday, May 24th 2019

Parkside, Regensburg, Germany

09:00 – 09:15 Opening remarks

Prof. Dr. M. Müller-Schilling, Prof. Dr. M. Acalovschi, Prof. Dr. I. Neumann-Holzschuh

09:15 – 10:30 Liver metabolism and pancreas

Chair: Prof. Dr. M. Müller-Schilling, Prof. Dr. Z. Sparchez

09:15 *Prof. Dr. Andreas Geier (Würzburg)*

NAFLD – The future of an old disease

09:30 *Prof. Dr. Monica Acalovschi (Cluj-Napoca)*

Management of alcoholic liver disease

09:45 *Prof. Dr. Sebastian Müller (Heidelberg)*

Survival in a 10 year prospective cohort of heavy drinkers: Liver stiffness is the best long term prognostic parameter

10:00 *Prof. Dr. Zeno Sparchez (Cluj-Napoca)*

Splenic embolization. Still a role in advanced liver cirrhosis?

10:15 *PD Dr. Stefan Fritz (Stuttgart)*

Pancreatic cystic neoplasms - an update

10:30 – 11:00 Coffee break

11:00 – 12:00 Endoscopy and ultrasound**Chair: Prof. Dr. S. Bataga, PD Dr. A. Kandulski, Prof. Dr. E. M. Jung***11:00 Prof. Dr. Roxana Sirli (Timișoara)*

Ultrasound for the diagnosis of cirrhosis complications

11:15 Prof. Dr. Ioan Sporea (Timișoara)

Contrast enhanced ultrasound for the evaluation of focal liver lesions

11:30 Prof. Dr. Simona Bataga (Targu Mures)

Prevention of gastric cancer and preneoplastic lesions

11:45 Prof. Dr. Marcel Tantau (Cluj-Napoca)

Therapeutic endoscopy 2019

12:00 – 12:45 Medical education, training and interprofessional research**Chair: Prof. Dr. Dr. h. c. W. G. Zoller, Prof. Dr. I. Sporea***12:00 PD Dr. Alexander Hann (Ulm)*

Digital tools for improvement of medical education

12:15 Dr. Stephan Schmid and Georg Niederalt (Regensburg)

Interprofessional projects in intensive care

12:30 PD Dr. Maria Neuss-Radu (Erlangen)

Modelling and Simulation of Epithelial Layers Controlling Transitions between Compartments in Organisms

12:45 – 14:00 Lunch break and poster viewing**Prof. Dr. M. Müller-Schilling, Prof. Dr. Dr. h. c. W. G. Zoller, PD Dr. K. Gülow, Dr. M. Grohmann, Prof. Dr. T. Schilling***Interactive cholangioscopy workshop*

PD Dr. Arne Kandulski (Regensburg)

Art exhibition: More than sonography – impressions

Prof. Dr. Ernst- Michael Jung (Regensburg)

Art exhibition: special figures

Rita Schwarzer

14:00– 15:00 GI-Oncology**Chair: Prof. Dr. S. Müller, Prof. Dr. P. Michl**

14:00 *Prof. Dr. Martina Müller-Schilling (Regensburg)*
Update HCC

14:15 *Prof. Dr. Patrick Michl (Halle/Saale)*
Pancreatic cancer, present and future

14:30 *Dr. Achim Jatkowski (Stuttgart)*
Efficacy of palliative chemotherapy in old patients with colon cancer

14:45 *Prof. Dr. Michael Sackmann (Bamberg)*
Advanced colorectal carcinoma: gastroenterological treatment options

15:00 – 15:45 Coffee break**15:45 – 16:45 Gut, IBD and infections****Chair: Prof. Dr. T. Andus, PD Dr. M. Selgrad, Prof. Dr. M. Diculescu**

15:45 *Dr. Maria Ciocirlan, Prof. Dr. Mircea Diculescu (Bucharest)*
IBD and microbiota

16:00 *PD Dr. Christian Schulz (München)*
Fecal microbiota analysis - ready for clinical applications?

16:15 *Prof. Dr. Adrian Goldis (Timișoara)*
Fibrosis in Crohn's disease - ways to diagnose, prevent and treat

16:30 *Prof. Dr. Tilo Andus (Stuttgart)*
New therapies in IBD

16:45 *Prof. Dr. Michael Jung (Mainz)*
Antibiotic prophylaxis in endoscopy

17:00 - 17:15 Closing remarks. Prof. Dr. M. Müller-Schilling, Prof. Dr. M. Acalovschi

Management of Alcoholic Liver Disease

Monica Acalovschi

Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Romania

While non-alcoholic liver disease (NAFLD) is probably the main cause of mild liver diseases globally, alcoholic liver disease (ALD) remains the most prevalent cause of advanced liver disease in Europe and USA and the main cause of liver-related mortality worldwide. Despite its profound economic and health impact, ALD has traditionally received little attention compared to the other three major liver diseases, HBV and HCV-related, and NAFLD [1], and little progress has been made in the management of patients with this severe clinical condition. Patients with ALD are mostly identified in advanced stages of the disease. Programs for early detection are scarce. The 28-day mortality of patients with alcoholic hepatitis (AH) still remains 20-40%. In severe AH, an acute deterioration of liver function combined with single or multiple organ failures was recently defined as acute-on-chronic liver failure (ACLF) [2]. The specific treatment of this complication remains unknown and liver transplantation in this setting is highly controversial.

The poor therapeutic progress in the field of ALD has, in part, resulted from the lack of experimental models of advanced ALD and from difficulties in performing clinical trials in patients with an active addiction. However, in the last years there has been renewed public and research interest in this severe liver disease, and ALD is receiving increasing attention by health authorities and the liver academic community [3]. Genetic and environmental risk factors for development of ALD have been studied. Animal models mimicking human AH have been evaluated for developing new drugs to treat AH. Studies are ongoing in order to identify molecular or non-invasive diagnostic tests for early recognition of significant ALD in patients with alcohol-use disorders (AUD). The number of transplantations for patients with ALD has increased over the past two decades [4]. It has been shown that hepatocellular carcinoma is often diagnosed in more advanced stages of ALD as compared to patients with HCV-related cirrhosis [5], although alcohol-consumption

accounts for around one-third of global incident cases of primary liver cancers. Clinical Practice Guidelines are now regularly issued by the major medical associations for the study of liver diseases – EASL [4], AASLD, ACG [6] in order to cover all these major issues in the management of the patients with ALD.

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Survival in a 10 year Prospective Cohort of Heavy Drinkers: Liver Stiffness is the Best Long term Prognostic Parameter

Sebastian Müller

Department of Internal Medicine, Salem Medical Center and Center for Alcohol Research, University of Heidelberg, Germany

Background & Aims: Alcoholic liver disease (ALD) is the most common liver disease in the western world. Although measurement of liver stiffness (LS) by transient elastography has been well established for early diagnosis of fibrosis, no prospective long-term data on survival exist so far in patients

with ALD. We here present the first data on the prognostic impact of LS on long-term survival of Caucasian heavy drinkers in a 10 year, prospective single center trial.

Method: Information of survival status was obtained in 675 (71.6%) of 943 screened patients that had presented for alcohol detoxification (6.0 days) over a 10-year period from 2007-2017 with a mean daily consumption of alcohol of 178 g. Mean observation time was 3.7 years and mean duration of heavy drinking was 14.0 years. All patients had LS measurements by transient elastography and routine laboratory tests.

Results: During the observation time, 106 patients (15.7%) died. The cause of death could be clarified in 42 patients (39%) and it was liver-related in 16 (38%). Overall death was highest associated with LS ($r=0.291$, $P=1.3E-14$), followed by hemoglobin and alkaline phosphatase (AP). In a multivariate proportional hazard model, LS next to age, AP and serum albumin was the most significant independent predictor of survival with a hazard ratio of 1.013 (1.003 to 1.023, $P<0.05$). Using ROC analysis, LS was the best predictor of death in general with an AUROC of 0.72 and a cutoff value of 14.0 kPa, followed by AP and albumin. Moreover, LS was the top predictor of death starting from 2 to 5 years. In contrast, LS was preceded by bilirubin and albumin in predicting one-year-survival. AUROCs to predict death for 1, 3 and 5 years were 0.76, 0.74 and 0.73, respectively, with corresponding cut-off values (Youden index) of 26.3, 14.0 and 6.4 kPa, respectively. When stratifying patients according to standard LS cut-off values <6 kPa, 6 to 12.5 kPa and >12.5 kPa, the survival curves were significantly different ($P<0.0001$). The 3-year survival rates were 94%, 88% and 74% and the 5-year survival rates were 90%, 78% and 64%, respectively.

Conclusion: We here identify LS as the best long-term prognostic parameter in patients who heavily consume alcohol. LS measurements should become an important parameter for the screening of alcoholics.

Partial Spleen Embolization

Zeno Sparchez

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Partial spleen embolization (PSE) is a minimally invasive angiographic intervention that has been developed for the treatment of severe thrombocytopenia due to hypersplenism. The procedure consists of the catheterization of one or more branches of the splenic artery with the injection of an embolic agent under angiographic guidance. It is highly effective when embolization of 50-80% of the splenic parenchyma is achieved. Platelet levels start to increase at 12-24h after the procedure and present a peak value at two weeks with a slight decrease afterwards. At two months the platelet level stabilizes, the value being two times higher than the baseline [1]. The indication for PSE is severe thrombocytopenia in patients with cirrhosis undergoing procedures with high risk of bleeding. Besides the increase in the blood cell count,

there have been reported other benefits of PSE in patients with cirrhosis, such as improvement of liver function [2], reducing the grade of hepatic encephalopathy [3] and benefits upon innate immunity [4]. Although the mechanisms of liver function improvement are not fully understood, it is suggested that a possible mechanism is the increased flux in the hepatic artery after PSE [5, 6]. Improved liver function has been observed in patients with hepatocellular carcinoma (HCC) undergoing combined local therapy, percutaneous ablation or transarterial chemoembolization with PSE, respectively, than local therapy for HCC alone [7, 8]. There is evidence that suggests the potential benefit of PSE in combination with esophageal variceal ligation (EVL), which has significantly reduced the rates of rebleeding compared to EVL alone [9]. In cirrhotic patients with recurrent variceal bleeding who are not suitable for transjugular intrahepatic portosystemic shunt (TIPS), PSE could be a treatment strategy to prevent rebleeding by reducing portal hypertension [10]. A recent study suggested a better 5-year patency of the intrahepatic stent in patients undergoing TIPS combined with PSE, than in those undergoing TIPS alone [11]. PSE has demonstrated its superiority over splenectomy in terms of morbidity and mortality due to its minimal invasiveness, thereupon it has been used as an adjuvant procedure before splenectomy, reducing complications and blood loss [12-14].

The complications that arise after PSE can be classified as minor and major. The minor complications occur in almost all patients and consist of left upper quadrant pain, intermittent fever, nausea, loss of appetite and vomiting, while major complications such as splenic abscesses, spontaneous bacterial peritonitis, pneumonia, pleuritis, splanchnic vein thrombosis occur in a lower proportion of patients. Severe complications are associated with Child Pugh C class and a large volume of embolized splenic parenchyma [15- 17].

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Pancreatic Cystic Neoplasms – an Update

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Pancreatic cystic neoplasms (PCN) are increasingly recognized in clinical practice due to the widespread use of modern abdominal imaging technologies. The most common PCN are the intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), and serous cystic neoplasm (SCN). While SCNs reveal a negligible risk of malignant transformation, IPMNs and MCNs display premalignant lesions.

For PCN, the clinical challenge lies in making the correct preoperative diagnosis and estimation of the malignant potential. Usually a combination of computed tomography, magnetic resonance imaging, and endoscopic ultrasound, eventually with fine needle aspiration are needed to reliable

assess the type and morphology of the cyst. Management of PCN should consider the prevention of malignant progression, while avoiding unnecessary pancreatic surgery.

A number of guidelines have been established in recent years in order to give treatment recommendations for PCN. However, most guidelines are not evidence-based and a clear consensus on the optimal treatment and follow-up strategy is lacking. Nevertheless, there remains a need for guidelines, even though they are currently based on expert consensus.

With regard to the guidelines of the European Study Group on Cystic Tumours of the Pancreas 2018, the revised Fukuoka Guidelines of the International Association of Pancreatology 2017, and the guidelines of the American Gastroenterological Association 2015, the following statements on the management of PCN can be made.

Generally, for all MCNs, surgical resection is indicated. Merely, the recent European guidelines consider surveillance for asymptomatic MCN <40 mm without risk factors such as mural nodules or cyst growth. In case of surveillance, a lifelong follow-up is recommended, every six months for the first year, then annually if no changes are observed.

For main-duct or mixed-type IPMNs with a dilation of the pancreatic duct >10 mm (Fukuoka guidelines) or ≥10 mm (European guidelines), surgical resection is warranted. For branch-duct IPMN, the risk of malignant progression is significantly lower. Some lesions can be safely followed while others require surgical resection. All three guidelines recommend surgery in case of jaundice, positive cytology, enhancing mural nodules ≥5 mm, or generally when a solid component is diagnosed. According to the European and/or Fukuoka guidelines, relative indications for surgery are seen for IPMNs with a cyst diameter >30 mm, for a pancreatic duct dilation of 5-9 mm, cyst growth, a thickened wall, an abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy, lymphadenopathy, or acute pancreatitis caused by IPMN. Furthermore, surgery can be considered for patients with an increased serum CA 19-9 level or new-onset diabetes.

Overall, the clinical management of PCN remains challenging. In each patient, the risk of malignant transformation has to be weighed against potential surgical morbidity. The indication for surgery should be made by an interdisciplinary team and pancreatic resection performed in an experienced high-volume center.

Ultrasound for the Diagnosis of Cirrhosis Complications

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Liver cirrhosis is the final stage of the majority of chronic liver diseases. Ultrasound (US) is the main imaging technique used for its diagnosis and follow-up. Gray-scale ultrasound can reveal typical aspects for diagnosis (irregular echo-

texture, irregular surface, the presence of ascites, ultrasound signs of portal hypertension etc.), but in early, compensated cirrhosis, the US aspect can be almost normal, and this is where ultrasound-based elastography techniques can be a real help, since their accuracy is higher than approximately 95% to diagnose cirrhosis.

Regarding cirrhosis complications, all the important guidelines underline the role of gray scale US in the screening for hepatocellular carcinoma (HCC), one of the most feared complications of cirrhosis. Once a nodule is found, it can be easily diagnosed by contrast enhanced ultrasonography (CEUS). EFSUMB guidelines on CEUS state that the most characteristic feature of HCC in liver cirrhosis is hyperenhancement in the arterial phase, followed by wash out in the late phase, a pattern encountered in more than 97 % of HCCs. Ultrasound based elastography can be also used as a predictor of HCC occurrence. Several studies have assessed the predictive value of liver stiffness (LS) values assessed by transient elastography (TE) for the presence of HCC. A significant increase in the risk of developing HCC that paralleled the increase of LS values was observed.

Gray-scale ultrasound can reveal signs of portal hypertension (PH), such as splenomegaly, splenic varices etc. Ultrasound based elastography can also be used to predict clinically significant PH (CSPH) measured by hepatic venous pressure gradient, as well as the presence of esophageal varices. The latest Baveno consensus accepts the use of TE in patients with virus related clinically advanced chronic liver disease to rule-in CSPH, patients with LS values by TE ≥ 20 -25 kPa being considered at risk of having endoscopic signs of PH. In addition, patients with a LS < 20 kPa and with a platelet count > 150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy.

In addition, gray scale US is the best way to search for ascites and to guide paracentesis for the diagnosis of spontaneous bacterial peritonitis.

In conclusion, multiparametric ultrasound (gray scale US, US based elastography, CEUS) is a useful and versatile tool to follow-up and diagnose complications of liver cirrhosis.

Contrast Enhanced Ultrasound (CEUS) for Focal Liver Lesions (FLL)

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Ultrasound is the most common imaging method, used by many specialties and for different regions of the body. Ultrasound of the liver is a good and sensitive method to detect lesions in the liver (focal liver lesions - FLL), but the specificity of the method is not very high. The introduction of contrast-enhanced ultrasound (CEUS), especially the second generation agents (with SonoVue), has improved the characterization of the hepatic lesions, making this method very competitive in comparison with CE-CT or CE-MRI [1].

Some international guidelines [2, 3] describe the indications and value of CEUS for different liver lesions. Two important studies, one that came from Germany [4], and another one from France [5] were published around 10 years ago, showing the value of CEUS for FLL diagnosis, taking CE-CT, CE-MRI or biopsy of the lesions as reference methods. These studies showed the accuracy of CEUS for different FLLs. But in the last years, the development of ultrasound has increased, and also the experience in using SonoVue.

The Romanian Society of Ultrasound in Medicine and Biology (SRUMB) decided to publish a more recent guideline regarding how to use CEUS in daily practice [6], being of real assistance for people performing this method. At the same time, because there are some centres with extensive experience in CEUS, SRUMB decided to have a prospective multicentre study on CEUS in FLL, using the model of German (DEGUM) or French (STIC) studies, but with a larger cohort of patients and using new generations of ultrasound machines. This prospective multicentre study has been finished now and the results have been sent for publication [7]. The results of this National prospective study comprised 2062 FLLs assessed by CEUS, from 14 Romanian centers with a good experience in CEUS (mostly performed in the Departments of Gastroenterology and Hepatology and some in Radiological Departments), over a 6-year period. Inclusion criteria for the study: newly diagnosed FLL on B-mode ultrasound, less than three lesions/patient, liver lesions evaluated by CEUS and by a second-line imaging technique (contrast enhanced CT or contrast enhanced MRI) or histology, considered as reference. From the 2062 FLL, 57.2% (1179) were malignant and 42.8% (883) were benign. Results of the study showed that in comparison with the reference method, CEUS had a sensitivity of 83.9%, a specificity of 97.8%, a positive predictive value of 98.1%, a negative predictive value of 82.2% and a diagnostic accuracy of 89.9% for the diagnosis of malignant lesions. For the benign lesions, CEUS had a sensitivity of 97.8%, a specificity of 83.9%, a positive predictive value of 82.2%, a negative predictive value of 98.1% and a diagnostic accuracy of 89.9%. But this study showed that the accuracy for different liver lesions is not the same, for example for hepatocellular carcinoma - 76.6% sensitivity, 98.4% specificity, and 91.2% accuracy, for hemangioma - 89.2% sensitivity, 99% specificity, and 96.9% accuracy and for liver metastases - 90.9% sensitivity, 98.4% specificity, and 96.9% accuracy. This study was performed in trained centers, all with a long and good experience in liver CEUS. All of them offered clinical information behind the CEUS examination, explaining the excellent performance of CEUS for FLL. The conclusion of the study was that CEUS is a good first line method for the assessment of FLL in daily practice.

CEUS for FLL showed in large multicenter studies and meta-analyses a good practical value [8]. For this reason, because of the low cost of the ultrasound contrast agent (and of the evaluation), accessibility, point of care method, absence of side effects or nephrotoxicity or irradiation (in comparison with other imaging methods), CEUS is a very interesting first line method for the evaluation of a new FLL discovered during ultrasound examination. If the CEUS pattern is not typical,

then other imaging methods or ultrasound-based biopsy will solve the case.

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Prevention of gastric cancer and preneoplastic lesions

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In spite of its declining incidence in the last years, gastric cancer (GC) is still the fifth most common cancer in the world, after lung, breast, colorectal and prostate cancer. However, GC is the third worldwide cause of mortality among all malignant diseases.

The prevention of GC includes the primary prevention: eradication of *Helicobacter pylori* (HP) and secondary prevention: detection, surveillance and/or treatment of the preneoplastic lesions.

In Romania we have no screening programme for HP, but it has been organized an important public awareness campaign.

The entire community of gastroenterologists, internal medicine specialists and general practitioners are now involved in detecting and treating HP infection.

Secondary gastric cancer prevention program is addressing to the patients with severe preneoplastic changes in the stomach. Population-based screening by endoscopy for detection of these preneoplastic lesions is implemented only in countries with a high incidence of gastric cancer, such as Japan and Korea. In the European countries, regular endoscopic follow-up is offered to patients with endoscopically visible preneoplastic lesions according to the MAPS recommendations. Identifying and surveillance of patients with gastric preneoplastic lesions leads to early diagnosis of gastric cancer, treatment options and an improvement in the survival rate.

The non-invasive screening is also possible with tests such as pepsinogen test (GastroPanel®).

In our experience in the First Gastroenterology Clinic from Târgu Mureș, between 2014-2018, 12,541 patients underwent upper digestive endoscopy. Patients with gastric cancer were excluded from the study. In all the patients, gastric biopsies and histopathological examination were made, and the OLGA classification was used. The histopathology examination revealed: in 5.55% atrophic gastritis, in 7.30% intestinal metaplasia and in 0.11% dysplasia. In 0.81% of the patients, polyps were detected and extirpated.

Active gastritis/pangastritis with HP infection was identified in 59.3% of the patients. The premalignant lesions were present mostly in the patients between 60 and 70 years, males and females being equally affected.

In summary, *Helicobacter pylori* infection was identified in more than half of our patients, indicating that it still has a high incidence in Romania. Women are as much exposed as men to present premalignant gastric lesions after 60 years. After the age of 60, it is worthy to screen the patients by endoscopy or to perform at least one non-invasive test such as pepsinogen (GastroPanel®), even in the regions with a low incidence of gastric cancer.

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Therapeutic Endoscopy 2019

Marcel Tantau

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Peroral endoscopic myotomy (POEM) procedure has more than 10 years experience [1] and now is becoming more and

more the standard of care for achalasia patients. The technique is now standardised and quality requirements have been developed for this procedure, while gaining more acceptance worldwide. In our hospital in Cluj we introduced the procedure more than 5 years ago [2].

POEM procedure was recently adapted to perform myotomy of the pylorus (G POEM from gastric) for gastroparesis, but also for other indications [3].

Zenker diverticula is a rare benign disease of the upper esophagus, treated with endoscopic treatment for almost 30 years, now with very good results [4]. But with the POEM technique (Z POEM), we can perform a complete myotomy of the pathological cricopharyngeal muscle.

Now, as endoscopists are managing very well the submucosal space (third space), the POEM technique has been extended to be applied for the resection of submucosal tumours with good results. The new technique is called tunnel resection: the mucosal entry is a couple of centimeters from the lesion and a submucosal tunnel is dissected up to the lesion. This is then completely dissected submucosally, and then extracted through another mucosal incision distally [5].

The presentation contains videos from our own experience with E POEM, G POEM, Z POEM and the submucosal tumors resection.

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Hepatocellular Carcinoma - Update

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Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and the third leading cause of cancer-related death worldwide (World Cancer Research Fund International). More than 90 % of HCCs arise in patients with underlying cirrhosis. Thus, the treatment approach of HCC depends on

the stage and extent of disease, the severity of the underlying liver disease and the overall performance status of the patient. Treatment consists of five strategies: 1. surgery (resection and liver transplantation), 2. locoregional procedures (ablation and transarterial embolization), 3. systemic therapies 4. immunotherapy and 5. best supportive care (BSC).

Especially, the systemic treatment for HCC has changed dramatically after the demonstration of a survival benefit with sorafenib in 2007 (SHARP trial and Asia-Pacific trial).

Currently, there are several first line - sorafenib and lenvatinib - and second line - regorafenib, cabozantinib and ramucirumab - treatments that have shown a survival benefit in HCC.

In a phase 3 trial (REFLECT), lenvatinib, a multikinase inhibitor, was non-inferior to sorafenib in overall survival in patients with untreated advanced hepatocellular carcinoma and represents an alternative to sorafenib in the first line setting.

In April 2017, the US Food and Drug Administration approved regorafenib for patients with HCC who have been treated with sorafenib and showed progress after treatment with first-line sorafenib. In a phase 3 trial (RESORCE), regorafenib significantly improved overall survival vs placebo.

Cabozantinib is a dual inhibitor of MET/VEGFR2 in tumors that has been shown in the phase 3 CELESTIAL trial to prolong overall survival in patients with advanced HCC who progressed on sorafenib.

Another category of agents that will provide new future treatment options are immune checkpoint inhibitors such as anti-PD-1/PD-L1 or CTLA-4 antibodies, which kill cancer cells via a unique mechanism of action, involving immune responses. The final results of the ongoing immunotherapy-based clinical trials for HCC are still awaited. Immunotherapy through immune checkpoint inhibition may have a large impact on HCC management in the future. In advanced HCC, PD-1 inhibition has shown clinical activity in second line and is now being tested in first line setting. In addition, combination therapy using an immune checkpoint inhibitor and a targeted therapy is another new therapeutic approach which is also currently under investigation.

In the CHECKMATE 040 trial, a phase I/II trial that enrolled patients with advanced HCC, nivolumab (an anti-PD1 agent) showed a manageable safety profile and a response rate of 20% with a median duration of response of 9.9 months in the dose expansion phase compared to a response rate of 15% for a median duration of 17 months in the dose-escalation phase. Based on these results, nivolumab was granted accelerated approval by the FDA for sorafenib-experienced HCC.

In May 2017, the FDA approved pembrolizumab for the treatment of any solid tumor confirmed to have high microsatellite instability or deficient mismatch repair. Pembrolizumab received accelerated approval by the FDA for sorafenib-experienced HCC based on an ORR of 17%, with a duration of response of ≥ 9 months reported in 77% of patients in KEYNOTE 224, a single-arm phase II trial that included patients after sorafenib progression or intolerance.

In addition, and of clinical relevance, single agents and combinations of immune checkpoint inhibitors are being tested in less advanced patients including patients in the intermediate and early stages.

In view of the new options in the treatment of HCC, adequate selection of a therapeutic strategy ideally based on specific biomarkers will become an important future challenge. For individualized patient care, genomic alterations identified in targetable genes will be useful to identify patients with HCC who could benefit from specific targeted therapy and immunotherapy. A major clinical challenge will be to evaluate the potential benefit of sequenced strategies or combinations between active agents and interventions.

Efficacy of Palliative Chemotherapy in Old Patients with Colon Cancer – based on Evidence or Gut Feeling?

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The number of old patients suffering from colorectal cancer is rising. However, old patients are severely underrepresented and in many cases actively excluded from clinical trials, which creates a lack of evidence for this growing group of patients. Furthermore, patients with advanced colorectal cancer are less likely to receive chemotherapy than younger patients. Among the patients treated, older patients are less likely to receive polychemotherapy or bevacizumab. Unsurprisingly, older colorectal cancer patients have been shown to be treated with less adherence to current treatment guidelines.

There is a limited number of published trials for old patients with colorectal carcinoma, most often retrospective or secondary analyses of existing study data. Most studies use 70 years of age as a discriminator for older vs. younger patients, although this value varies among the published sources. In general, the available data suggest that common substances – 5FU, oxaliplatin, irinotecan and bevacizumab – are as beneficial in older patients as they are in the younger ones in terms of cancer control, while results regarding toxicity are inconsistent. Notably, there are no studies comparing old and younger patients treated with anti-EGFR agents.

Nominal age alone is probably not the best marker to predict chemotherapy tolerance. Not only is there a paucity of evidence for old patients, but definitions of what constitutes an old patient are inconsistent varying from >65 to >80 years of age. Additionally, other markers to assess fitness or biological age are available, for example geriatric assessment tools or comorbidity indices. Although helpful in some situations, the value of these methods to make sound treatment decisions for old patients with advanced colorectal cancer remains unclear.

Advanced Colorectal Carcinoma: Gastroenterological Treatment Options

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In patients with colorectal carcinoma (CRC) stage IV, gastroenterological treatment includes nutritional recommendations, treatment of opioid-induced constipation, endoscopic interventions for bleeding or obstruction, and in the individualized antitumor therapy.

Nutrition: A recent trial showed a survival benefit in patients with a high intake of plant food as compared to animal products, both before and after the diagnosis of advanced CRC. Another study revealed that coffee intake of more than one cup per day was associated with a significantly reduced CRC-specific mortality.

Opioid-induced constipation: About 40% of CRC patients suffer from opioid-induced constipation. It shows a higher prevalence in CRC patients than nausea. A recent meta-analysis indicated that μ -receptor antagonists and prucaloprid may be beneficial.

Malignant obstruction: Endoscopic stenting for malignant colonic obstruction will be successful technically as well as clinically in 90-98% of patients. Adverse events appear to be rare. According to several trials, survival is similar to that after emergency operation for colonic obstruction.

Tumor bleeding: Endoscopic measures include injection therapy, clipping, coagulation, and application of hemostatic agents.

Chemotherapy: Oncologic therapy in advanced CRC nowadays is applied individualized to the specific patient. In selecting the chemotherapeutic agents, age, co-morbidity, tumor spread, molecular markers, and localization of the CRC in the right or left colon are to be considered. Karnofsky index or ECOG status are essential in selecting the individual chemotherapy. Median survival in CRC stage IV has been improved tremendously. Unlike in other cancers, immunotherapy of CRC has been successful only in a small minority of patients so far. Recent research aspects include also the modulation of the intestinal microbiome in CRC patients. Furthermore, the intestinal virome very recently has been shown to significantly influence CRC patient survival.

Summary: Patients with CRC stage IV benefit from individualized therapy. Recent advances in CRC research show very promising results. Nutrition has a significant influence on survival. Endoscopic interventions for bleeding or obstructing tumors could avoid surgery in many cases.

IBD and Intestinal Microbiome - Use and Misuse of PPI and Antibiotics

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Inflammatory Bowel Diseases (IBD) develop as a result of an aberrant inflammatory response to intestinal pathogens in

genetically susceptible subjects. Changes in the gut microbiome have been recognized as promoting factors in both Crohn's Disease (CD) and Ulcerative Colitis (UC).

Composition of gut microbiota is sensitive to various endogenous and exogenous factors, such as the type of delivery at birth, genetics, diet, history of infection or medication. Among these, we seem to be witnessing a global sustained use of proton pump inhibitors (PPIs) and antibiotics. Chronic use of PPIs leads to a reduction of *Fecalibacterium prausnitzii* (considered potentially protective against IBD), while consecutive alkalinization of the gastric milieu is a risk factor for *Clostridium difficile* diarrhea. Therefore, when administering PPI, CD and UC patients could be prone to more frequent hospital admissions and disease flares.

Regarding antibiotics, their usage in IBD remains a paradox. On one hand, fluoroquinolones and metronidazole have been linked to trigger a new onset of CD, especially in pediatric populations. It appears that the infant's microbiome is dynamic and easily susceptible to changes until it reaches maturation, thus the need for antibiotherapy at an early age may be a risk factor for later IBD. On the other hand, antibiotics are a well-recognized treatment line in specific cases of IBD and one mechanism of action might be improvement of dysbiosis. Following this hypothesis, a Romanian medical research team found that rifaximin used as an adjunctive treatment in CD patients could help achieve a more prolonged clinical remission than standard treatment alone, possibly by mediating anti-inflammatory pathways and increasing *Fecalibacterium prausnitzii* and *Bifidobacterium* spp.

Taken together, PPI and antibiotics comprise different regimes for the eradication of *Helicobacter pylori* (Hp) infection. Previous data has suggested that new onset IBD might occur during the first 6-12 months after Hp eradication using a clarithromycin-based triple therapy, while the presence of Hp would be protective against new onset IBD. A recent Romanian study supports the negative association between Hp infection and IBD. The protective effect of Hp infection might be explained by the T cell mediated immunological tolerance against different allergens and limited inflammatory response. Eradication of Hp infections does not appear to significantly alter the shortterm course of IBD.

We would conclude that the gut microbiota represents a viable rich habitat, going through sometimes unpredictable changes under the influence of various factors. We should carefully prescribe medications such as PPI or antibiotics and patients should be closely monitored at all times.

Fibrosis in Crohn's Disease: from Diagnosis to Treatment

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A severe complication of long-lasting and recurring bowel inflammation that can occur in Crohn's disease is represented by fibrosis-associated strictures, which in time can cause

bowel obstruction. Due to this, around 80% of the patients with Crohn's disease will have to perform at least one major bowel surgery during their lives, with high rate of recurrence of the fibrotic strictures afterwards. The distinction between the inflammation-related bowel wall thickening which may respond to anti-inflammatory therapy and the fibrostenotic stricture which is unresponsive to any of the current drugs is often difficult. There are several histopathological changes in the fibrogenic mechanism that appear in the fibrosis-associated strictures. The most important in this process is the expansion of mesenchymal cells including fibroblasts, myofibroblasts and smooth muscle cells.

The diagnosis of the fibrosis-associated strictures is often difficult, because all noninvasive methods used cannot distinguish properly fibrosis from inflammation. Although it is difficult, several methods can be used to diagnose fibrosis: ultrasound based elastography, CT scan or MRI.

The treatment of fibrostenotic strictures is limited. On medical treatment, the recurrence rate of fibrosis-associated strictures is quite high, despite of the chosen therapy. Recent studies which investigated the role of Interleukin (IL) 36 antibodies seem to be optimistic regarding a new possible therapy that can be used for prevention and treatment of intestinal fibrosis in patients with inflammatory bowel diseases. IL 36 represent a group of cytokines in the IL1 family that are involved in the regulation of fibrogenesis in fibroblasts. Unfortunately, further data is needed to support this theory. In selected patients, another therapy that can be performed is endoscopic dilation. In patients that underwent this procedure, the success rate of the first dilation was 97%, with a 5% rate of serious complications. During the disease course, it is estimated that 46% of the patients will benefit from a new procedure of dilation. An alternative to endoscopic dilation is surgical resection. It is considered that 24% of the patients require a new surgical procedure. In order to establish the risk factors for development of the fibrosis-associated strictures, several biological and endoscopic parameters, such as the level of C-reactive protein or the endoscopic disease activity have been studied, with no results so far.

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Inflammatory Bowel Disease – New Therapies

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Medical treatment with corticosteroids has led to a normalization of the life expectancy of patients with inflammatory bowel disease beginning around 1960. 5-Aminosalicylic acid and immunosuppressive therapies, such as thiopurines and mercaptopurine have allowed successful maintenance treatment. At the beginning of the 21st century, monoclonal antibodies against tumor necrosis factor was the next important step of medical treatment. Meanwhile biosimilars have been made available for infliximab and adalimumab to reduce the cost of the treatment.

What are the next steps of medical treatment? Three main targets are addressed by new drugs or soon available drugs in the pipeline from the big pharmaceutical companies.

1. Interleukin-12/Interleukin-23 antibodies

The first of this group is Ustekinumab, which binds to the p40 subunit shared by both IL-12 and IL-23. Ustekinumab was first introduced to treat psoriasis and psoriatic arthritis successfully.

In Crohn's disease it induced remission in up to 40% of TNF-antibody naïve patients and in up to 21% of the pretreated patients (UNITI-1 and UNITI-2). In the maintenance study IM-Uniti remission was held in up to 63% and 41%, respectively, in TNF naïve or pretreated patients. This led to approval by the EMA in September 2016 for Crohn's disease patients.

Now the results of the first phase III-studies with Ustekinumab in ulcerative colitis patients are available showing induction or remission in up to 16% (placebo 5%) and maintenance of remission in up to 44% (placebo 24%). EMA-submission was filed in December 2018.

Another antibody against the p19-subunit of IL-23 selectively inhibiting IL-23, called MEDI2070 or Brazikumab (700 mg i.v. at week 0 and 4) was tested in Crohn's disease patients in a phase 2a-study resulting in clinical remission in up to 28% of the patients (placebo 16%).

Another antibody against the p19-subunit of IL-23 selectively inhibiting IL-23, called Mirikzumab was studied in a phase II-study in patients with moderately to severely active ulcerative colitis leading to clinical remission in up to 26% in the 200 mg dose group (placebo 5%).

2. Inhibition of intracellular signaling by Janus-kinase-inhibitors

Janus kinases are very important for the intracellular signaling from cytokine receptors to the nucleus in

inflammation. Tofacitinib was the first small molecule JAK-inhibitor acting against JAK 1-3 and first approved for rheumatoid arthritis.

After showing clinical remission in ulcerative colitis patients in up to 18% (placebo 8%) in the phase-III induction studies OCTAVE-1 and OCTAVE-2 and maintenance of remission in up to 41% in the OCTAVE-sustain trials using 2 x 5-10 mg/d orally, it was approved for ulcerative colitis in the EU in June 2018.

Two phase IIb studies have been published in Crohn's disease, which evidenced no statistically significant benefit.

A JAK-1-inhibitor, Filgotinib showed a significant benefit of 47% clinical remission (placebo 23%) in a phase II-study in patients with Crohn's disease in the FITZROY study after 32 weeks treatment with 200 mg/d orally.

Another JAK-1-inhibitor, Peficitinib showed in a phase IIb dose-finding study in patients with ulcerative colitis a significant benefit of 28% clinical remission (placebo 7%) after 8 weeks treatment with 150 mg/d orally.

A third JAK-1-inhibitor, Upadacitinib demonstrated in a phase IIb dose-finding study in patients with ulcerative colitis a significant benefit of 20% clinical remission (placebo 0%) after 8 weeks treatment with 45 mg/d orally.

The same JAK-1-inhibitor showed in a phase IIb dose-finding study in patients with Crohn's disease a significant benefit of 27% clinical remission (placebo 7%) after 16 weeks treatment with 2 x 6 mg/d orally.

Thus we may have soon several JAK-inhibitors for the treatment of both Crohn's disease and ulcerative colitis.

3. Inhibition of lymphocyte trafficking

The first of this class agent approved in the EU was Vedolizumab which induced remission in 17% (placebo 5%) after 300 mg Vedolizumab at week 0 and 2 in patients with ulcerative colitis. Maintenance of remission was achieved in 42-25% (placebo 16%) for Vedolizumab every 4 or 8 weeks.

In Crohn's disease Vedolizumab induced remission in 15% (placebo 6%) after 300 mg Vedolizumab at week 0 and 2. Maintenance of remission was achieved in 36-39% (placebo 22%) for Vedolizumab every 4 or 8 weeks.

The next drug in this class is Etrolizumab, inhibiting both a4b7/MAdCAM-1-mediated lymphocyte trafficking to the gut mucosa and aEb7/E-cadherin-mediated lymphocyte retention in the intraepithelial space. In a phase-II study, Etrolizumab led to remission rates of up to 21% (placebo 0%) in patients with ulcerative colitis. Etrolizumab was much more effective (44% remission rate) in TNF-antibody-naïve patients compared to patients pretreated with TNF-antibodies (5%).

Another a4b7-antibody Abruimab (1 x 210 mg or 70 mg every 4 weeks) showed in a phase IIb-study in patients with ulcerative colitis remission rates of up to 13% (placebo 4%) after 8 weeks.

Another target of lymphocyte trafficking is MAdCAM-1. The anti-MAdCAM-1-antibody SHP647 showed in the TURANDOT study in patients with ulcerative colitis clinical response rates up to 16% (placebo 3%). In the OPERA study in patients with Crohn's disease remission rates have been up to 30% after 12 weeks (placebo = 23%).

Another new method of inhibiting the migration of lymphocytes is via sphingosine-1 phosphate receptor targeting. The egress of lymphocytes from lymph nodes is dependent on the S1P gradient, whose concentration is higher in blood than lymph nodes and effector tissues.

S1PR agonists induce long-lasting receptor downregulation and lymphocyte sequestration in lymphoid tissues and inhibit transendothelial migration of T cells across the lymphatic endothelial barrier in the lymph node, where they remain sequestered.

The first drug studied was Ozanimod, an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5, which induces peripheral lymphocyte sequestration, potentially decreasing the number of activated lymphocytes circulating to the gastrointestinal tract.

In the phase II trial TOUCHSTONE, Ozanimod at a dose of 1 mg/d led to a remission rate of 57% (placebo 37%) after 8 weeks and a maintenance rate of 21% (placebo 6%).

Conclusion: we probably will have soon some new drugs for the treatment of inflammatory bowel disease inhibiting IL-12/23-signalling, inhibiting JAK-signaling and inhibiting lymphocyte trafficking. However, the group of patients who still are unable to respond to new drugs is still much too large to be happy with the current situation. And we must also hope that no new severe side-effects will occur with the new treatments.

With the larger armamentarium of drugs, treatment of patients with inflammatory bowel disease will become more effective but also more complicated and demanding in the future.

LIST OF POSTERS

1. Endoscopic foreign body recovery. A retrospective analysis of the years 2013-2018

Alexander Mehrl, Merlin Küchle, Arne Kandulski, Martina Müller-Schilling, Kilian Weigand

University Hospital Regensburg, Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology, Rheumatology, Immunology and Infectious Diseases, Regensburg, Germany

2. Case series on endoscopic RFA in GAVE stomach

Alexander Mehrl, Merlin Küchle, Arne Kandulski, Martina Müller-Schilling, Kilian Weigand

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3. Gastritis cystica profunda with macroscopic aspect of gastric cancer treated with endoscopic mucosal resection in unoperated stomach in a patient after heart transplant surgery

Lidia-Sabina Cosma, Arne Kandulski, Kilian Weigand, Martina Müller-Schilling

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4. Prognostic factors and comparative outcomes in ulcer vs non-ulcer acute upper gastrointestinal bleeding, a single tertiary center experience

Monica Pantea¹, Septimiu Voidazan², Anca Negovan¹, Melania Macarie¹, Minodora Schiopea³, Anne-Marie Enache³, Kinga Szakacs-Hajnal⁴, Ciorba Marius³, Simona Bataga¹

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5. The causes and risk factors for non-variceal bleeding in patients with cirrhosis

Daniela Matei^{1,2}, Ioana Groza¹, Sergiu Pasca², Bogdan Procopet^{1,2}, Lidia Munteanu^{1,2}, Marcel Tantau^{1,2}

1) Regional Institute of Gastroenterology and Hepatology Prof. Dr. Octavian Fodor; 2) Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

6. Risk factors for early mortality in variceal bleeding

Andreea Barbulescu, Iulia Ratiu, Ioan Sporea, Mirela Danila, Alina Popescu, Raluca Lupusoru, Roxana Sirli

Department of Gastroenterology and Hepatology, Victor Babes University of Medicine and Pharmacy Timisoara, Romania

7. Life threatening gastrointestinal emergencies in elderly patients: The emergency physician's perspective

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8. Analysis of patients with sepsis in an interdisciplinary Emergency Department. Implications and tools for nursing practitioners for an early detection by suspected sepsis

Ann-Cathrin Meyer, Sebastian Grau, Eva Noel, Ingrid Heinric, Berthold Petri

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9. The value of ultrasound in modern emergency departments

Alexander Krohn, Mathias Bauer, Matthias Ott, Johannes Heymer, Christian Menzel, Tobias Schilling

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10. Mortality is 4-5 times higher for abdominal pain than for chest pain: An analysis of mortality and chief complaints in a German emergency department
Matthias Ott, Lisa Vogelsang, Tobias Schilling
 Department of Emergency Medicine, Klinikum Stuttgart – Katharinenhospital, Stuttgart, Germany
11. Influence of strict and relaxed definitions of video capsule retention on the retention rate
Achim Jatkowski, Wolfram G. Zoller
 Klinikum Stuttgart, Allgemeine Innere Medizin und Gastroenterologie, Hepatologie, Infektiologie und Pneumologie, Katharinenhospital, Stuttgart, Germany
12. Celiac disease: an unusual case of gluten-sensitive enteropathy
Vlad Pavel, Stephan Schmid, Martina Müller-Schilling
 Internal Medicine I, Gastroenterology, Endocrinology, Rheumatology, Infectiology, Emergency Medicine, University Hospital Regensburg, Regensburg, Germany
13. The effect of *Lactobacillus plantarum* on 5-Fluorouracil induced intestinal mucositis in Wistar Rats
Lidia Ciobanu^{1,2}, Diana Maria Oancea¹, Cristian Berce¹, Dan Vodnar³, Alexandru Meşter¹, Sorina Onica¹, Cristian Tefas^{1,2}, Marian Taulescu⁴
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14. A rare case of desmoplastic small round cell tumor in a young adult
Marc C. Sora¹, Tudor Mocan², Zeno Sparchez^{2,3}
 1) Polissano Clinic, Sibiu; 2) Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca; 3) Regional Institute of Gastroenterology and Hepatology, 3rd Medical Department, Cluj-Napoca, Romania
15. Immune-mediated hepatitis (IMH) due to checkpoint inhibitor Pembrolizumab in a patient with a history of multiple malignant melanoma
Michaela Hohenester, Sophie Schlosser, Martina Müller-Schilling
 University Hospital Regensburg, Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology, Rheumatology, Immunology and Infectious Diseases, Regensburg, Germany
16. Diverse imaging patterns in NET liver metastasis: case reports and literature review
Ioana Duca, Zeno Sparchez, Mircea Dragoteanu, Dan Lucian Dumitrascu
 Iuliu Hatieganu University for Medicine and Pharmacy Cluj-Napoca, Romania
17. Neuroendocrine cells density alterations in colonic mucosa of patients with inflammatory bowel disease
Corina Meianu¹, Gabriel Becheanu^{1,2}, Mona Dumbrava¹, Carmen Preda^{1,2}, Alexandra Naiden-Moise¹, Alexandru Petraru¹, Tudor Stroie¹, Carmen Plaisanu¹, Dan Pitigoi¹, Mircea Diculescu^{1,2}
 1) Fundeni Clinical Institute, Gastroenterology Department; 2) Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
18. Outcome of anti-TNF discontinuation in patients with IBD: a prospective observational study on a series of cases
Corina Meianu¹, Gabriel Becheanu^{1,2}, Mona Dumbrava¹, Carmen Preda^{1,2}, Alexandra Naiden-Moise¹, Alexandru Petraru¹, Tudor Stroie¹, Carmen Plaisanu¹, Dan Pitigoi¹, Mircea Diculescu^{1,2}
 1) Fundeni Clinical Institute, Gastroenterology Department; 2) Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
19. Management of aseptic splenic abscesses as extraintestinal manifestation of Crohn's disease - Immunosuppressive therapy with Infliximab instead of splenectomy in a 25 year old patient
Viktoria Nitzl, Sophie Schlosser, Michael Selgrad, Martina Müller-Schilling
 University Hospital Regensburg, Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology, Rheumatology, Immunology and Infectious Diseases, Regensburg, Germany

20. Alteration of serotonin expressing neuroendocrine cells in colonic mucosa of patients with inflammatory bowel disease
Corina Meianu¹, Gabriel Becheanu^{1,2}, Mona Dumbrava¹, Carmen Preda^{1,2}, Alexandra Naiden-Moise¹, Alexandru Petraru¹, Tudor Stroe¹, Dan Pitigoi¹, Carmen Plaisanu¹, Mircea Diculescu^{1,2}

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21. A study on the quality of life in patients with irritable bowel syndrome
Anne-Marie Enache¹, Minodora-Maria Schiopea¹, Ilie-Marius Ciorba¹, Monica Pantea², Melania Macarie², Dan Georgescu², Simona Bataga²

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22. New onset of ascites after delivery as a first sign of recurrent colorectal cancer with peritoneal carcinomatosis in a young female patient

Lidia-Sabina Cosma¹, Stefan Brunner², Martina Müller-Schilling¹, Arne Kandulski¹

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23. Diagnostic accuracy and therapeutic efficacy of digital single-operator cholangioscopy for biliary lesions and stenosis
Kilian Weigand, Merlin Kuchle, Ina Zuber-Jerger, Martina Müller-Schilling, Arne Kandulski

University Hospital Regensburg, Department of Internal Medicine I, Gastroenterology, Endocrinology, Rheumatology and Infectious Diseases, Regensburg, Germany

24. A case of cholangioscopy assisted stenting of the common bile duct

Voicu Mercea, Lidia Ciobanu, Dana Matei, Marcel Tantau

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25. Intraductal Tubular Papillary Neoplasm (ITPN) – a new kid on the block of epithelial pancreatic neoplasms and precursor of pancreatic cancer

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**Endoscopic foreign body recovery.
A retrospective analysis of the years 2013-2018**

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Background: Foreign body recovery of accidentally or intentionally ingested objects is a common reason to counsel the endoscopist, especially in on-call service.

Patients and Methods: We evaluated all endoscopic foreign body retrievals at our department in the years 2013-2018. As a primary endpoint was the technical success, which was considered as successful endoscopic removal of the foreign body. As secondary endpoint, the number and type of complications were examined.

Results: A total of 75 cases were evaluated. In 25 cases (33%) the ingestion was accidental and in 50 cases (67%) foreign bodies were ingested on purpose. A total of 65 gastroscopies, 4 enteroscopies, 1 sigmoidoscopy and 5 colonoscopies were performed. In 39 cases (52%), intubation was necessary, in 24 cases an overtube was used (32%) for removal of the foreign body and in 8 cases (11%) a protective cap was used. In 72 cases (96%), an endoscopic removal of the foreign bodies was possible. In 3 cases a surgical intervention was necessary. No major complications were reported in our cases.

Conclusion: The endoscopic intervention to remove foreign bodies is a safe and successful method.

Case series on endoscopic RFA in GAVE stomach

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Background: Gastric antral vascular disease (GAVE) syndrome is a known cause of gastrointestinal bleeding and

iron deficiency anemia. Argon plasma coagulation Beamer Therapy (APC) is an established treatment method. However, there are patients who do not respond adequately to APC. Here we present our results using radio frequency ablation (RFA) in patients with GAVE stomach.

Patients and Method: We retrospectively evaluated four cases of patients (two men and two women, 54-75 years) with persisting indication for blood transfusion despite more than three performed APC therapies. Cirrhosis was present in two patients and haemophilia B in one patient. Only the patient with haemophilia showed compromised coagulation. One patient had ischemic cardiomyopathy with the need for lifelong platelet aggregation inhibition. In advance, 5-17 APC treatments were performed per patient.

Results: RFA therapy was performed 1-4 times until complete macroscopic eradication of the GAVE lesions. Therapy was performed with the Barrx system using the 90-9100 ablation catheter. Already after the first RFA there was no further need for blood transfusions in all patients. There were no major or minor complications in all procedures.

Conclusion: RFA appears to be an effective method of treatment of GAVE stomach in the case of APC failure.

Gastritis cystica profunda with macroscopic aspect of gastric cancer treated with endoscopic mucosal resection in unoperated stomach in a patient after heart transplant surgery

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Background: Gastritis cystica profunda (GCP) is a rare gastric lesion with an unknown pathogenic mechanism, consisting of cystic dilation of the gastric glands extending into the submucosa. GCP is considered a benign lesion, but there is controversy about its malignant potential. We report a case of GCP in a 67-year-old man with immunosuppression after heart transplant surgery.

Case description: A 67-year-old man with no known family history of gastrointestinal disorders or malignant diseases presented for follow-up four months after heart transplantation and complained of persistent abdominal pain, loss of appetite and weight loss since a few weeks. The upper gastrointestinal endoscopy revealed a 20mm diameter large ulcer of the angulus, dysplastic mucosal lesions with irregular pit pattern, neovascularization and vesicular expansions reaching along the lesser curvature to the anterior gastric wall, and gastric corpus atrophy. The narrow-band imaging (NBI) endoscopy showed abnormalities suggesting gastric cancer, and the endoscopic ultrasonography visualized a gastric wall thickening up to 11mm with distortion of the normal layers up to the muscularis propria, but no enlarged lymph nodes. An endoscopic mucosal resection (EMR) was performed and multiple biopsies were taken. The histological analysis revealed an unusual form of chronic gastritis with foveolar hyperplasia with cystic lesions, mucus retention, marked mucosal oedema and mild eosinophilia in polypoid lesions, without *H. pylori* infection or dysplasia. The laboratory tests showed a positive CMV and HSV 1/2 serology, and normal pepsinogen levels. The control endoscopy after three and six months revealed a significant improvement, with the histological finding of a mild chronic gastritis with mild eosinophilia and multiple small cysts, without evidence of malignancy.

Discussion: Although the exact pathogenesis of GCP is unknown, injury and inflammation of the mucosa are thought to be the central mechanism. It is considered that the disruption of the muscularis mucosae allows migration of epithelial cells into the submucosal layer and subsequent cystic dilation. GCP was initially thought to be benign; however, more recently, GCP has been considered to be a possible precancerous lesion, after reports of dysplastic changes within the submucosal glands of select cases of GCP. The findings of a heterogeneously enhancing polypoid lesion with cystic components on EUS should raise the suspicion for GCP. Previously, gastric resection was the treatment of choice, but more recently, EMR and endoscopic submucosal dissection (ESD) have become the therapeutic modalities of choice. In the case of our patient, the lesion was resected using EMR without complications, avoiding an unnecessary surgical resection.

Conclusions: The diagnosis of GCP remains challenging despite the current advances in endoscopic technique, and current debate exists about its biological behavior and malignant potential. The advances in the endoscopic techniques like the development of EMR and ESD are useful in establishing a diagnosis and avoiding unnecessary surgery.

Prognostic factors and comparative outcomes in ulcer vs non-ulcer acute upper gastrointestinal bleeding, a single tertiary center experience

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Background & Aim: Gastrointestinal bleeding is a common problem encountered in the emergency department. With a mortality rate up to 10%, rapid assessment, hemodynamic stabilization and evaluating the risk of rebleeding and complications are essential for case management. Aim of the study was to evaluate the nonvariceal gastrointestinal bleeding (NVUGIB), to compare outcomes between ulcer and non-ulcer bleeding, to identify risk factors and to uncover differences in bleeding severity, baseline characteristics or procedures of care.

Material and Methods: A consecutive series of 297 patients with non-variceal upper gastrointestinal bleeding were included in our study. The patients were referred for gastroenterological examination and upper digestive endoscopy between 2017-2018 in the Gastroenterology department from Targu-Mures, Emergency County Hospital. Demographical data, emergency endoscopy findings and questionnaires regarding drug exposure and previous medical conditions were applied to all subjects, and evaluated for statistical analysis.

Results: We divided the subjects in a study group of 195 patients with ulcer-related bleeding (75 females and 120 males) and a control group of 102 non-ulcer bleeding (39 females and 63 males) with ages between 20 - 96 years. The mean age of the patients was not significantly different between these two groups (66.86±14.72 years vs. 68.82±13.84 years, p=0.368). Gender (p=0.98) and age (p=0.58) were not significant risk factors for severe endoscopic lesions in both ulcer and non-ulcer group. Glasgow- Blatchford score (GBS) was calculated for each group (12.29±3.25 vs 12.79±3.68) at admission, with similar results. In the ulcer group, a GBS > 15 points was associated with a statistically significant risk for severe endoscopic lesions (according to Forrest classification) with endoscopic hemostasis required (p=0.0001; OR: 4.59; 95% CI 1.76-11.9). The ulcer-related bleeding lesions had higher odds of in-hospital mortality (p=0.021; OR: 3.22; 95%CI 1.24-8.53). Partial gastrectomy was a significant risk factor (p=0.030) for severe endoscopic lesion in both ulcer and non-ulcer group, according to Blatchford score and Forrest classification. A total of 128 patients from both groups received gastrotoxic drugs (15-AINS; 36-antiplatelets; 74-anticoagulants) with a GBS > 13 associated with higher odds for blood transfusion (p=0.016; OR: 2.91; 95%CI 1.15-7.37) due to severe anemia. Associating aspirin (75-150mg) and oral anticoagulants had a higher risk of severe endoscopic lesion development, with the need for endoscopic hemostasis in ulcer bleeding group (p=0.034). No significant (p>0.05) differences regarding the lesion severity scores were noticed between antivitamin K users and non-vitamin K antagonist oral anticoagulants (NOACs: apixaban, dabigatran, rivaroxaban) users in either group.

Conclusions: This study found that GBS >15 significantly correlated with likelihood of requiring endoscopic therapy in both groups. Patients with ulcer-related gastrointestinal bleeding had worse outcomes than those with non-ulcer bleeding, with high odds of in-hospital mortality. No differences

in the severity scores and prognosis were noticed between the different types of oral anticoagulants in both groups.

The causes and risk factors for non-variceal bleeding in patients with cirrhosis

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Background & Aims: The causes of upper gastrointestinal bleeding (UGIB) in patients with cirrhosis can be grouped into two categories: the first one includes lesions which occur as a consequence of portal hypertension (gastroesophageal varices and portal hypertensive gastropathy), and the one second includes lesions also observed in the general population (peptic ulcer, erosive gastritis, reflux esophagitis, Mallory-Weiss syndrome, tumors etc.).

The aim of this study was to evaluate the causes of non-variceal bleeding in patients with cirrhosis and to assess the risk factors for non-variceal bleeding.

Method: We analyzed the data from all the patients who came to the emergency department of a tertiary medical center presenting upper gastrointestinal bleeding (UGIB) and cirrhosis in a 12-month period. Preendoscopic, endoscopic and postendoscopic management of these patients has been conducted in accordance to the international guidelines. The study population was divided into two groups (with non-variceal and with variceal bleeding) and the following parameters were assessed: NSAIDs and/or antiplatelets use, history of variceal bleeding, ascites, encephalopathy, MELD score, comorbidities, hemoglobin (g/dl), thrombocytes (no. elements/mm³), INR (international normalized ratio), total bilirubin (mg/dl) and creatinine (mg/dl) levels.

Results: 236 patients with cirrhosis and UGIB were included in the study. Non-variceal bleeding was present in 30.3% of the cases. The causes for non-variceal bleeding were the following: peptic ulcer 57%; erosive lesions (esophagitis, gastritis, duodenitis) 15.2%; portal hypertensive gastropathy 11.4%; Mallory Weiss syndrome 8.9%; tumors 3.8%; and Dieulafoy lesions 3.8%.

Comparing the two groups of patients (with non-variceal and variceal bleeding), the following differences were observed: NSAIDs and/or antiplatelets use 26.6% vs 13.6% (p=0.018); history of variceal bleeding 12.7% vs 41.8% (p<0.001); ascites 44.3% vs 73.9% (p<0.001); encephalopathy 25.3% vs 29.9% (p=0.546); MELD score 15.8±4.4 vs 16.7±5.7 points (p=0.240); ≥2 comorbidities 21.5% vs 8.7% (p=0.007); hemoglobin(g/dl) 9.5±2.6 vs 9.1±2.2 (p=0.206), thrombocytes (no. elements/mm³) 114,000 (74,900; 153,000) vs 101000 (70,250;130,000) (p=0.024), INR 1.51 (1.27;1.80) vs 1.66 (1.44;2.00) (p=0.002), total bilirubin(mg/dl) 1.6 (1.0;3.4) vs 2.2 (1.4;4.2) (p=0.006), creatinine (mg/dl) 0.68 (0.60;1.00) vs 0.75 (0.61;1.02) (p=0.916).

Conclusion: Non-variceal bleeding was present in 30.3% of the cases. The most common cause of non-variceal bleeding in patients with cirrhosis was peptic ulcer. Non-variceal bleeding was more frequently correlated with NSAIDs and/or antiplatelets use, the association of at least two comorbidities, while variceal bleeding was more frequently associated with a history of variceal bleeding, ascites, thrombocytopenia, prolonged INR and hyperbilirubinemia.

Risk factors for early mortality in variceal bleeding

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Background & Aim: Acute haemorrhage from ruptured esophageal varices (EV) is probably the most serious consequence of uncontrolled portal hypertension in cirrhotic patients, with a significant mortality. Overall survival is improving, due to new therapeutic approaches and improved medical care. However, early mortality after an episode of acute variceal bleeding remains high. The aim of this study was to evaluate the risk factors affecting the 5-day mortality rate after acute variceal bleeding in unselected cirrhotic patients.

Material and Method: 537 cirrhotic patients admitted in our department with variceal bleeding were evaluated: 351 men and 186 women, with a mean age of 58.8 years, during a 7 years period. We divided the patients into three groups: group A, patients who died due to severe variceal bleeding (n=32), group B, the survivors (n=452), and group C, patients who died from other complications (n=53). We tried to identify the prognostic factors for massive, uncontrollable variceal hemorrhage by comparing patients' characteristics of the three groups.

Results: Global in-hospital mortality rate was 15.8% (n=85), with a death rate of 5.9% (n=32) due to severe bleeding, while

Table I. Characteristics of the study patients

Characteristics	Group A (32p) vs. Group B (452p)	Group A (32p) vs. Group C (53p)
EV grade III	11/32 vs. 195/452 p= NS	11/32 vs. 22/53 p= NS
EV grade II	20/32 vs. 257/452 p= NS	20/32 vs. 31/53 p= NS
Age	58 y/o vs. 59 y/o p= NS	58 y/o vs. 59 y/o p= NS
Child Pugh Class C	22/32 vs. 151/452 p=0.0006	22/32 vs. 31/53 p= NS
Meld score	24.5 vs. 17.4 p= 0.0005	24.5 vs. 24.8 p= NS
Severe thrombocytopenia	10/32 vs. 76/452 p< 0.0001	10/32 vs. 11/52 p= NS
Haemorrhagic shock	24/32 vs. 12/452 p< 0.0001	24/32 vs. 13/53 p= NS

9.8% of patients died from other complications. There were no significant differences neither regarding the proportion of grade 3 EV and grade 2 EV in group A vs. group B vs. group C, nor regarding the mean age (Table I). The proportion of Child Pugh class C patients in group A was significantly higher than in group B, but similar to group C. The MELD score was significantly higher in group A than in group B patients, but similar to group C. Severe thrombocytopenia (<50,000/mm³) and haemorrhagic shock at admission were significantly more frequent in group A than in group B, but were similar to group C.

Conclusion: Liver failure, severe thrombocytopenia and haemorrhagic shock at admission were the risk factors identified in this study for in-hospital 5-day mortality rate due to variceal bleeding.

Life threatening gastrointestinal emergencies in elderly patients: The emergency physician's perspective

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Background & Aim: The number of elderly patients presenting to the emergency department is expected to increase in the next decades. There is an increasing body of evidence that intensive care treatments in elderly patients may be futile in certain circumstances. A shared decision making process regarding life sustaining therapies should be based on knowledge about the expected clinical course. In this study, we aimed to follow up the elderly patients with life threatening gastrointestinal emergencies, who were admitted to the intensive care unit. The information obtained in this study should help clinicians to estimate the magnitude of this issue and may serve as valuable background information while counselling patients and families.

Methods: We conducted a retrospective study to identify the patients ≥ 80 years of age admitted via the interdisciplinary emergency department at the Klinikum Stuttgart, Katharinenhospital to the intensive care unit (ICU) in the years 2016 and 2017. These data were derived from the emergency department's information system. A single chart review of the electronic medical record of each individual patient was performed to identify the primary diagnosis at admission. All patients with a primary diagnosis from the field of gastroenterology were included in the study. In these patients, data regarding treatment, age, sex, length of hospital stay, in hospital death and transfer to palliative care was analyzed.

Results: In the two year period, approximately 70,000 patients presented to our emergency department. We identified 248 patients ≥80 years of age who were admitted to the intensive care unit. Out of these patients 19 (6 female, 13 male) had a

leading diagnosis from the field of gastroenterology. Diagnoses included gastrointestinal bleeding (12 patients), sepsis with hepatobiliary focus (6 patients) and liver failure (1 patient). Mean age at presentation was 84.3 years (± 3.6 years, range 80.1-92.7 years), mean length of stay was 14.8 days (± 10.7 days, range 1.3- 38.6 days). Six patients required mechanical ventilation (2 patients non- invasive ventilation, 4 patients invasive ventilation), 9 patients received catecholamines. In-hospital death occurred in 5 (26.3%) patients. Two of these patients received invasive ventilation. In 4 patients therapy was transferred to palliative care before death.

Conclusion: While medical problems associated with frailty are a major issue in medical practice, elderly patients with life threatening gastrointestinal emergencies account only for a small proportion of the patients presenting to our emergency department. Due to the small number of cases included in our study, all results have to be interpreted with caution. Gastrointestinal bleeding is the most frequent diagnosis in this selected group of patients. In-hospital death was prevalent with a rate of 26.3% in the entire group and a rate of 50% in the subgroup of patients that received invasive ventilation. The high proportion of patients demanding a transition to palliative care before death underlines the importance of the provision of adequate information in the process of shared decision making. Further research is required to analyze the functional and longterm outcomes.

Analysis of patients with sepsis in an interdisciplinary Emergency Department. Implications and tools for nursing practitioners for an early detection by suspected sepsis

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Background & Aim: Sepsis is the 3rd leading cause of death within developed countries. Despite modern and state-of-the-art medical facilities as well as advanced medical treatment plans sepsis still seems to be a ‚silent killer‘. The survival rate of septic patients correlates directly with the time from diagnosis to the first initiation of i.v. antibiotics. Therefore, it is essential for the nursing and medical staff to recognize red flags criteria regarding sepsis. Since patients seek emergency consult with a variety of symptoms in an emergency department, it is necessary for the nursing practitioners, as they are the forefront of patient care, to detect a potential septic patient as fast as possible in order to initiate adequate treatment.

Method: Motivated to decrease the in-hospital mortality rate of patients diagnosed with sepsis, we conducted a retrospective analysis of patients who were admitted to the hospital and were diagnosed with sepsis. The analyzed time period was about a year, from July 2016 until June 2017. The study included 119 patients who were treated in the emergency

department first and got along admitted as in-patients to the hospital.

Results: On the one hand it was important to know to which medical discipline the patient was admitted after the initial emergency treatment. The numbers showed that most of the patients had a nephrological cause (28.6%) and went to a nephrological unit. Closely followed by another 27.7% of patients who were admitted to the gastroenterological specialty. Another 18.8% had an oncological cause, 8% and urological cause, and 11.6% needed intensive care treatment. On the other hand, we evaluated how these patients were discharged from the hospital. It was recorded that 62.5% of the patients were discharged to their homes; 11.6% were discharged to special health care facilities and 4.5% were discharged to another hospital as well as rehabilitation facility. Nevertheless, 20.5% of the patients died during their in-patient stay in our hospital. Moreover, 57% of the patients who needed intensive medical treatment died on the intensive care units. Putting the numbers in context and perspective, it can be said that the mortality of sepsis is higher than the mortality of a STEMI. In addition to the retrospective analysis, we implemented the qSOFA Score (quick Sepsis related Organ Failure Assessment) as an assessment tool for every staff-member of the emergency department. The idea was to raise the staff's awareness about the warning signs of sepsis and therefore hand them an uncomplicated supportive tool to make an early detection regarding sepsis. It was supposed to fasten the process, including the drawing of baseline blood cultures and urine samples, from the assumption of possible sepsis until the initiation of the first i.v. antibiotic.

Conclusion: The qSOFA-Screening was well received by the staff and became a standard procedure. Future examinations will test the effect of qSOFA on the outcome of sepsis treatment.

The value of ultrasound in modern emergency departments

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Background & Aim: Emergency Ultrasound is becoming an increasingly important tool in acute and emergency medicine. Ultrasound allows us to take almost instant decisions on potential critically ill patients in the emergency room (ER). Ultrasound is always immediately available, it is fast, effective, with focus on the patient medical needs. Ultrasound will bring benefit to nearly every patient group in the ER. It can be crucial for decisions in Trauma, Cardiovascular Disease, Pulmonary Diseases, Obstetrics and Gynaecology and it can help to provide vascular access.

Methods: In this study, we analysed Ultrasound use in the Interdisciplinary Emergency Department (INA) at Klinikum Stuttgart – Katharinenhospital since 2011. We analysed questions such as the percentage of patients undergoing

emergency Ultrasound, their age, the medical question, the experience of the examiner, the normal and pathologic finding, the diagnoses as well as the resulting clinical steps. We followed the patient's history regarding the correctness of the initial diagnosis, the repeat of the Ultrasound during the hospitalization and complementary imaging. Furthermore, we analysed correctness of the conclusions drawn from the ultrasound.

Results: Our retrospective data are showing increasingly impact of Ultrasound in modern Emergency Medicine. The possibilities of Ultrasound as harmless, easy to learn and always available diagnostic tool leads to an increasing use of Ultrasound in our ED since 2011. It was most commonly used in patients with abdominal discomfort (33%), followed by dyspnea (13%) and trauma (12%). The results of the emergency Ultrasound could be confirmed in 94% in the following therapy and diagnostics. The diagnostic potential was independent of the clinical experience of the examiner. The treating physician was able to derive an acute treatment decision from the sonographic findings in 41% of the cases. Emergency Ultrasound could reduce further diagnosis. In 64% of cases the finding of emergency ultrasonography is believed, in 42% of them without further diagnostics. In two-thirds of cases, the initial emergency sonographic diagnosis is sufficient for complete therapy or further diagnostics at the ward and the hospitalization of the patient is shortened. The specificity of this emergency sonography was 99.2%, correlated to the main discharge diagnosis.

Conclusions: These results demonstrate the enormous importance of emergency ultrasonography for the diagnosis and the further course of treatment. Therefore, a doctor working in an emergency room should have a good knowledge of ultrasonography. Furthermore, we and other could show that Ultrasound is relatively easy to learn and train in an ED. We started to establish an Ultrasound training under specialist and senior medical supervision in our Department and will furthermore verify our initial findings.

Mortality is 4-5 times higher for abdominal pain than for chest pain: An analysis of mortality and chief complaints in a German emergency department

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Background & Aim: Besides dyspnoea and traumatic injuries, abdominal pain and chest pain are very frequent chief complaints in emergency departments. Treatment and differential diagnosis of abdominal pain can be very challenging. Other studies describe rates of mortality for abdominal pain at about 5.1% during hospital treatment. Our study aims to determine the most frequent chief complaints in our emergency department and their mortality during hospital stay.

Methods: We performed a retrospective data analysis of patients in a large German emergency department (ED) with about 100 to 120 patients a day. In our ED, with a few exceptions patients are 18 years and older. Data has been collected from two different time periods, November 2009 to January 2010 and November 2012 to January 2013. We excluded outpatient cases and analyzed the chief complaint at presentation and death during hospital stay.

Results: In total 2,032 inpatient cases - 1,214 (59.7%) male and 818 (40.3%) female - were analyzed. On average patients were 59.5 years old. Besides limb pain (11.7%), abdominal pain (11.1%), chest pain (9.0%) and dyspnoea (9.0%) are the most frequent chief complaints. Mortality during the hospital stay was highest with general condition deterioration (12.1%). Abdominal pain (3.1%) showed higher mortality than chest pain (1.1%). Following a subanalysis, abdominal pain was an unspecific chief complain regarding the discharge diagnosis.

Conclusions: National and international studies show similar rates of chief complaints in the emergency department. Some studies show even higher mortalities for abdominal pain compared to our results. Analogous to other studies, mortality of abdominal pain exceeds chest pain during hospital stay. One possible reason for lower mortality in chest pain could be standardized care and extensive research. This may underline the need for further research, time critical treatment and standardized care of the challenging, although unspecific, chief complain abdominal pain.

Influence of strict and relaxed definitions of video capsule retention on the retention rate

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Background & Aim: Video Capsule endoscopy (VCE) is often the first diagnostic imaging test for many small bowel pathologies including small bowel bleeding, Crohn's disease and tumours, both benign and malignant. Though generally safe, VCE has clinically significant risks, foremost the risk of capsule retention and in some cases subsequent bowel obstruction. The published rates of capsule retention are inconsistent among different studies and range from 0.75 to 21 percent. This variation is largely due to differences in the patient collectives (i.e. patients with or without Crohn's disease); different definitions of capsule retention may also play a role. So far, different definitions have not been directly compared to each other in one patient collective.

Methods: All VCE in our hospital (n=146) from 01.01.2016 to 22.03.2019 were retrospectively evaluated for different quality parameters, including rate of passage into the colon, small bowel transit time, main findings and ability to answer the clinical question. All cases without passage into the colon were followed up regarding a possible retention fitting one of three definitions.

Results: the different definitions of capsule retention and their corresponding retention rates were: 1) Strict definition: "Colon not reached during recording time and capsule excretion not proven" (6.2%); 2) Standard definition: "Retention anywhere in the GI-tract for more than two weeks or need for intervention" (3.4%); 3) Relaxed definition: "Retention in the small intestine and need for an intervention" (2.1%).

There were five cases without sufficient or timely proof of capsule excretion as the only indication of retention counted under the strict definition. Four cases of secondary endoscopic placement due to prolonged gastric passage were not counted as retention.

Conclusion: Capsule retention is a relevant complication of video capsule endoscopy. In our hospital, retentions were rare and could be resolved endoscopically. In order to compare different studies, the exact definition of a capsule retention should always be stated.

Celiac disease: an unusual case of gluten-sensitive enteropathy

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Background: Celiac disease is an autoimmune disease of the small intestine, which is characterized by a gluten intolerance / wheat allergy. In Germany, about 800,000 people are affected by this disease. Most cases are undiagnosed. The symptoms are manifested by ailment in the gastrointestinal tract, nutritional deficiencies, unspecific fatigue, joint pain and growth disorders in children. The consequence is a chronic inflammation of the small intestine as well as a regression of the intestinal villi. This results in different nutrient deficiencies as fewer nutrients can be absorbed by the degenerated villi. The severe acute onset of celiac disease, also called celiac crisis, is very unusual and not well documented in adults. Although celiac crisis is a life-threatening complication of celiac disease, only about 20 cases have been reported in the literature so far.

Case Presentation: Here we report the case of a 24-year-old female patient with a severe course of celiac disease. The patient presented with one-month diarrhea and vomiting followed by malabsorption syndrome with weight loss, anasarca, electrolyte imbalance, bicytopenia, coagulation disorder and elevated transaminases. The patient never had gastrointestinal symptoms before and noticed only occasionally slight peripheral edema. Massively increased transglutaminase IgA antibodies have been detected. Endoscopically an atrophic duodenal mucosa could be observed. Histologically, a lymphocytic duodenitis, suitable for celiac disease, was diagnosed. There was no evidence of lymphoma. Colonoscopy was normal. A haemogram showed anemia and hemolysis. Also, heat antibodies could be detected by the Coombs test. The patient was admitted to the intensive care unit for surveillance. After transfusion of an erythrocyte concentrate, an increase in hemoglobin was seen. Bradycardia

was observed several times, however without clinical relevance. There was no evidence of endocarditis in either transthoracic or transesophageal echocardiography. After starting a gluten-free diet, calcium and folic acid substitution, a satisfactory clinical response was achieved. Also laboratory chemistry showed a clear improvement. After two weeks of intensive care, the patient was transferred to the normal ward.

Conclusion: Celiac crisis is a rare first appearance form of celiac disease characterized by severe diarrhea, dehydration, weight loss, hypoproteinemia and metabolic and electrolyte imbalance. Despite its rarity, celiac crisis should be considered in patients with apparently unexplained chronic diarrhea. In earlier case reports, authors have used corticosteroids as therapy. However, over time it became clear that the early detection of celiac disease followed by gluten-free diet is significantly better in these patients. The risk of a refeeding syndrome should be evaluated upon introduction of a gluten-free diet. There were no complications observed concerning our patient.

The effect of *Lactobacillus plantarum* on 5-Fluorouracil induced intestinal mucositis in Wistar rats

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Background & Aims: Some previous studies reported that probiotics could modulate the microbiota and decrease the severity of chemotherapy-induced mucositis. This study assessed the potential protective effect of *Lactobacillus plantarum* (*L. plantarum*) on 5-Fluorouracil (5-FU)-induced intestinal mucositis in Wistar rats.

Methods: Twenty-one Wistar rats were divided into three groups of seven animals (F, L, M). Group L received for 9 days 3.32×10^9 CFU/ml of *L. plantarum* orally. On the 7th day of the experiment 400mg of 5-FU was administered intraperitoneally in groups L and F. Group M received only the vehicles. All animals were sacrificed on day 9. At the end of the experiment, the viability of lactic acid bacteria from faeces samples was determined by plate count method. A semi-quantitative histological assessment of duodenum, jejunum and colon was obtained by rating 11 histological characteristics of mucositis from 0 (normal) to 3 (severe). The independent groups were analyzed using the Kruskal-Wallis test, Mann-Whitney U-test or Student's t-test.

Results: At the end of the experiment, the mean viability of lactic acid bacteria from faeces samples was similar between

groups M and L (4.72 ± 2.40 CFU/ml vs. 4.78 ± 3.54 ufc/ml). In the group F, the mean viability of lactic acid bacteria was lower (2.80 ± 1.92 ufc/ml), but without reaching statistical significance comparing with group L ($p=0.09$) or M ($p=0.58$). In the group F, the most affected areas were the jejunum (median histological score 25) and the duodenum (median histological score 22). The colonic degenerative lesions were moderate (median histological score 12.5). In the group receiving *L. plantarum*, significantly fewer degenerative lesions were depicted on the colon mucosa ($U = 0$; $p = 0.006$) and the duodenum ($U = 3.5$; $p = 0.033$). Microscopic degenerative lesions in the jejunum were less severe in the group L, but without reaching statistical significance ($U = 7.5$; $p = 0.159$).

Conclusions: In the group of rats that received *L. plantarum* before and after 5-FU administration, the mean viability of lactic acid bacteria was similar with the control group. Fewer microscopic degenerative lesions were depicted in this group on the colon and duodenum mucosa comparing with group receiving only 5-FU.

A rare case of desmoplastic small round cell tumor in a young adult

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Background: Desmoplastic small round cell tumor (DSRCT) is a highly aggressive and rare mesenchymal tumor that develops in the abdominal cavity of primarily young males. There are around 450 cases reported since 1991 and diagnosis is based on histological analysis of biopsies showing small round blue cells in nests separated by an abundant desmoplastic stroma [1, 2]. DSRCTs contain a unique reciprocal translocation $t(11:22)(p13;q12)$ that involves the EWSR1 and WT1 genes [3]. Prognosis is poor and management of DSRCT remains a challenge because current therapeutic schemes lack a significant cure rate despite the use of aggressive treatments [2].

Case Presentation: We present the case of a 32-year-old white male, who was admitted for bloating and distention of the abdominal cavity with a two month history. He had no past medical history or a family history and denied smoking, drug or alcohol consumption. Physical examination revealed a distended abdomen with a positive fluid wave test. Laboratory results showed slight leukocytosis, an increase in ESR and the ascitic fluid had a SAAG of 0.7, presenting mesothelial atypia on cytology. Upon performing abdominal ultrasound we found ascites, multiple intraperitoneal masses, with the dominant one measuring 7/4 cm, and pleural nodules. After an ultrasound guided biopsy from the peritoneal masses histological analysis with immunohistochemistry revealed a DSRCT. Staging was performed using a CT scan with intravenous contrast, which showed multiple peritoneal and mesenteric masses,

omental cake sign, metastatic retroperitoneal and mediastinal adenopathies and bilateral pleural metastasis, leading to the diagnosis of a stage IV DSRCT according to the Peritoneal Cancer Index [4]. Treatment with Doxorubicin and Ifosfamide was started and after multiple paracenteses the patient developed metastasis at the puncture sites. The patient survived for 5 months after diagnosis.

Conclusion: This case highlights the poor prognosis and limited therapeutic opportunities for this extremely rare and aggressive cancer type.

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Immune-mediated hepatitis (IMH) due to checkpoint inhibitor Pembrolizumab in a patient with a history of multiple malignant melanoma

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Background: Some tumors express PD-L1 and PD-2, which bind the PD-1 receptor on T-cells and inactivate T-cell function. Pembrolizumab inhibits the PD-L1 receptor on T-cells and helps to restore the immune response against tumor cells. This leads to an increasing long-term survival, especially in patients with tumors producing high levels of PD-L1. Pembrolizumab is approved for treating melanoma, non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma, urothelial cancer and head and neck squamous cell carcinoma (HNSCC). Unfortunately, Pembrolizumab can cause severe immune-related side effects.

Case Report: In this case report, we present a 73-year old patient with pre-diagnosed multiple malignant melanoma, who developed immune-mediated hepatitis grade 2 following therapy with Pembrolizumab. The patient was diagnosed with malignant melanoma of the left abdomen in 2012 (AJCC

2009: pT1a). The patient underwent resection. In 08/2017 another malignant melanoma of the left lower leg was detected (AJCC 2009: pT2b, pN1 (1/1), cM0, stage IIIA). After resection, the patient received adjuvant immunotherapy with Pembrolizumab. After 12 cycles the patient reported increasing symptoms of fatigue in July 2018. Lab results revealed an increase of transaminase levels (AST 108 U/l (< 50); ALT 105 U/l) as well as cholestasis [γ GT 556 U/l (< 60); AP 556 U/l (45-117), bilirubin 2.3 mg/dl (0.2 - 1.0)]. CRP was slightly elevated. Acute viral infection [hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis E (HEV), cytomegalovirus (CMV), Epstein-Barr-Virus (EBV), varicella-zoster-virus (VZV), human herpes virus 6 (HHV-6), parvovirus B19], vascular diseases and nutritive-toxic causes could be excluded. Anti-nuclear antibody (ANA) titer level was elevated up to 1:640 (<1:80) with nuclear dense speckled pattern (AC-2). There was no hint for primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) or IgG4-associated disease. Liver parenchyma was echo-inhomogeneous in ultrasound. Pembrolizumab-mediated autoimmune hepatitis was diagnosed and treatment with cortisone pulse therapy initiated. Pembrolizumab was discontinued. Liver values decreased immediately. Prednisolone was slowly reduced. After four months of corticoid therapy, liver test values normalized in November 2018 and cortisone could be stopped.

Conclusion: Patients receiving immunotherapy with Pembrolizumab should undergo close monitoring of liver enzymes. In case of Pembrolizumab-mediated hepatitis, corticosteroids should immediately be initiated. Prednisolone doses should be tapered until liver values normalize. Indications for Pembrolizumab are expected to increase. Therefore, gastroenterologists and hepatologists should be aware of immune-mediated side effects.

Diverse imaging patterns in NET liver metastasis: case reports and literature review

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Aim: to identify the imaging patterns of metastases from different digestive neuroendocrine tumors (NET) and to realise a literature review.

Methods: Three patients with the final diagnosis of liver metastases from carcinoid neoplasia (gastric, ileal, rectal) underwent clinical and biological examination, and were investigated by ultrasound (US-grey-scale, Doppler, contrast-enhanced US), scintigraphy (colloid and red-blood cell-labeled SPECT, liver angioscintigraphy), contrast-enhanced CT, MRI and liver-biopsy with consecutive histology.

Results: We present the cases of three young patients (34-47 years old) that were referred with the following complaints: astenia (1), weight loss (2), abdominal pain (1) and rectorrhagia (1). Laboratory data showed cholestasis (2), hepatic cytolysis

(1), slight anemia (1), respectively normal parameters (1). Liver US detected hypo- and anechoic masses (gastric NET), hyperechoic and hypervascular (gastric NET), multiple cysts inside a hyperechoic mass (ileal NET) and cysts with solid component (rectal NET). Liver angioscintigraphy detected high hepatic perfusion index (45-85%) on the projection area of the tumors, suggesting malignancy. Contrast-enhanced CT revealed atypical cysts (2/3 patients) and only in 1 patient it suggested metastases. In one case of suspicion of polycystic liver disease, MRI did not detect any enhancement, pleading for hamartomatosis. Histologic examination, together with endoscopic investigations, confirmed the NET origin of the liver metastases.

Conclusion: NET liver metastases have different imaging patterns, some are cystic, others are hypo- or hyperechoic. Thus one should be aware of that variability of presentation encountered in this disease.

Neuroendocrine cells density alterations in colonic mucosa of patients with inflammatory bowel disease

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Background & Aims: Several published studies on human and animal models showed increased densities of neuroendocrine cells (NE) cells in colonic mucosa of inflammatory bowel disease (IBD). The aim of our study was to determine the NE cells densities in colonic mucosa of patients with IBD in our Department.

Methods: Colonic biopsies from 18 patients with IBD (8 with ulcerative colitis, 10 with Crohn's disease) and 16 healthy controls were evaluated histopathologically with hematoxylin-eosin staining and immunohistochemically with chromogranin A (CgA) and synaptophysin (Syn) antibodies.

Results: NE cells were counted on a total median number of 24.1 (7,56) crypts for CgA, 24 (5,57) for Syn in IBD group and 29 (11,64) crypts for CgA and 29.2 (11.52) crypts for Syn in controls. The total densities/subject of NE cells were significantly higher in the IBD group compared to controls for both CgA and Syn: 1.45 (0.72,2.78) and 0.86 (0.43,1.73) for CgA ($p=0.006$), 0.89 (0.22,1.63) and 0.63 (0.28,1.28) for Syn ($p=0.025$). According to the type of IBD we obtained a median number of NE cells/crypt for UC of 1.33 (0.92,2.66) for CgA, 0.88 (0.5,1.32) for Syn and 1.48 (0.72,2.78) for CgA and 0.89 (0.22,1.63) for Syn for CD, $p=0.89$ and $p=0.9$, respectively. The median NE cells densities were analysed according to disease duration as follows: disease duration of less than 4

years 1.53 (0.8,2.78) for CgA, 0.95 (0.68,1.63) for Syn, disease duration of more than 4 years 1.37 (0.72,2) for CgA and 0.87 (0.22,1.43) for Syn, $p=0.33$, $p=0.093$, respectively. According to the endoscopic activity of the disease the median NE cells densities were 1.36 (0.72,2.78) for CgA, 0.87(0.22,1.63) for Syn in the segments with endoscopic activity and 1.43 (0.72,2.78) for CgA and 0.88 (0.2,2.78) for Syn in the segments with quiescent colitis, $p=0.26$ and $p=0.8$, respectively).

Conclusion: Our study showed an increased density of CgA and Syn positive NE cells in patients with IBD as compared to controls.

Outcome of anti-TNF discontinuation in patients with IBD: a prospective observational study on a series of cases

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Background: Anti-TNF alpha therapy can be stopped in inflammatory bowel disease (IBD) patients with sustained clinical remission at 1 year. About 50% of patients show a relapse within 1 year and more than 80% achieve the response and have no adverse events after restarting the same anti-TNF treatment.

Patients and Methods: We performed a prospective observational study on 11 patients with IBD: 4 with Crohn's disease (CD) and 8 with ulcerative colitis (UC), in whom we stopped anti-TNF therapy for sustained clinical and endoscopic remission. All patients were treated with anti-TNF therapy in monotherapy and were in sustained clinical and endoscopic remission for a mean period of 4.72 years (range 2-8). All patients were deescalated on conventional treatment and followed on a mean period of 9.63 months (range 5-19).

Results: 9 patients (81.8%) maintained clinical remission on a mean period of 10.5 months. Two patients relapsed at 5 and 9 months, respectively. One patient who relapsed had the therapeutic drug level before stopping the anti-TNF agent. Retreatment of relapse with the same anti-TNF agent was effective (both patients responded) and safe.

Conclusions: In our series of patients with IBD in whom we stopped the biological agent for sustained clinical and endoscopic remission, 81.8% of patients maintained long-term clinical remission. Retreatment with the same anti-TNF agent was safe and effective. Predictive factors for relapse are required for the optimal selection of patients in whom stopping the biologicals is safe for long term maintained clinical remission.

Management of aseptic splenic abscesses as extraintestinal manifestation of Crohn's disease - Immunosuppressive therapy with Infliximab instead of splenectomy in a 25 year old patient

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Background: Crohn's disease is a subtype of inflammatory bowel disease (IBD). In contrast to ulcerative colitis, it can affect the entire gastrointestinal tract discontinuously. Typical symptoms include diarrhea and abdominal pain. Common complications are fistulas, abscesses, and stenosis. Extraintestinal manifestations are common, e.g. affected are eyes (iritis, uveitis), joints (sacroiliitis), or the skin (erythema nodosum, pyoderma gangrenosum). Here we describe a case of Crohn's disease with aseptic splenic abscesses as a very rare extraintestinal manifestation.

Case Presentation: A 25 year old man was admitted to another hospital with a two-month history of pain in the left lower abdomen, nausea, regurgitation, fatigue, weight loss and fever. His medical history revealed an initial diagnosis of Crohn's disease in 2011, at the age of 18. He had previously been treated with mesalazine and/or prednisone and azathioprine, by which he developed acute pancreatitis. His defecation was unchanged, three times a day with slime but without blood coverage. During an inpatient stay at the onset of his symptoms an abdominal ultrasound scan revealed three hypoechoic splenic lesions, suggestive of splenic abscesses. Aspiration of one abscess proved to be sterile. The patient was treated with Piperacillin/Tazobactam and oral application of prednisone (60mg daily) and was discharged with a reduced dose of prednisone (20mg daily). His condition failed to improve. Two weeks later a repetition of the ultrasound scan displayed progression of the abscesses. Therefore, a splenectomy was recommended. Based on the recommendation the patient came to our hospital to get a second opinion. An elevated white blood cell count of 14.72/nl, C-reactive protein (CRP) of 110 mg/l and microcytic hypochromic anemia (9.9g/dl) with iron deficiency was determined. Blood cultures as well as coprocultures were repeatedly negative. Crohn's disease staging (MRI, colonoscopy, gastroscopy) revealed mild inflammatory activity. Cytomegalovirus was histopathologically negative. Abdominal ultrasound scan and computer tomography (CT) showed a splenomegaly with three splenic abscesses (11x6cm, 7.6x4.6cm, 7.2x5.7cm). Intravenous prednisone (1mg/kg) application was initiated with dual antibiotic protection (Meropenem, Metronidazol). The CRP level rapidly decreased. However, size of the splenic abscesses remained stable. With the objective of avoiding splenectomy, the treatment was changed to application of 5mg/kg Infliximab. After three administrations of Infliximab up to now the patient demonstrated symptomatic improvement. Another ultrasound scan revealed a decrease in

size of the splenic abscesses (4.1x3.3cm, 4.8x3.8cm, 5.7x4.2cm). The CRP level remained negative.

Conclusion: Aseptic splenic abscesses are a very rare extraintestinal manifestation of Crohn's disease, which may precede, occur during or follow acute episodes of the disease. Here we show that treatment with immunosuppressive medication such as Infliximab can lead to symptomatic improvement, indicated by reduction or disappearance of aseptic splenic abscesses due to Crohn's disease and avoid splenectomy or percutaneous drainage. Treatment with Infliximab displays only few adverse events (transient fatigue and diarrhea, no fever, no severe infection). Thus, continuation of this regimen is promising.

Alteration of serotonin expressing neuroendocrine cells in colonic mucosa of patients with inflammatory bowel disease

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Background & Aims: There have been described increased mucosal densities of serotonin (5-HT) positive neuroendocrine (NE) cells in inflammatory bowel disease (IBD).

The aim of our study was to evaluate serotonin positive NE cell densities in colonic mucosa of patients with IBD.

Methods: Colonic biopsies from 18 patients with IBD (8 with ulcerative colitis, 10 with Crohn's disease) and from 16 healthy controls were evaluated histopathologically after hematoxylin-eosin staining and immunohistochemical staining with serotonin antibodies.

Results: NE cells positive for 5-HT were counted on a total median number of 20.7 (1.80) crypts in IBD group and 25.65 (2.64) crypts in controls. The total densities/subject of 5-HT positive cells were significantly higher in the IBD group compared to controls: 0.56 (0.11,1.87) for the IBD group and 0.28 (0.14,0.71) for controls, p=0.004.

According to the type of IBD, we obtained a median number of 5-HT positive cells/crypt for UC of 0.7 (0.23,1.87) for UC and 0.51(0.11,0.98) for CD, p value=0.16.

When we compared the densities of 5-HT positive cells between the patients with clinically active disease and the patients in clinical remission we found a median density of 5-HT positive cells of 0.59 (0.49,1.87) and 0.5 (0.11,1.17) in patients with clinically active disease and patients in clinical remission, respectively, p value=0.2.

According to endoscopic activity the median 5-HT densities were 0.72 (0.49,1.48) in patients with endoscopic active disease and 0.54 (0.11,1.87) in patients with endoscopic remission p=0.12.

Conclusion: Our study showed an increased density of serotonin positive neuroendocrine cells in IBD colitis when compared to healthy controls.

A study on the quality of life in patients with irritable bowel syndrome

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Background & Aim: Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain or discomfort associated with altered bowel habits in the absence of structural abnormalities. IBS is one of the most commonly encountered gastrointestinal disorders, with an estimated global prevalence of 11.2%; the severity of symptoms varies and can considerably reduce the quality of life (QOL). The aim of this study was to analyze the impact of IBS on the QOL and to identify the differences regarding demographic data. We also evaluated the construct validity and internal consistency of the Romanian version of the Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire.

Material and Method: Patients diagnosed with irritable bowel syndrome, based on Rome IV criteria were enrolled in this study. Demographic data and the standardized IBS-QOL questionnaire were registered in all subjects. The IBS-QOL survey consists of 34 items, each with a five-point response scale that measures eight domains found to be relevant to patients with IBS. To evaluate the internal consistency of the questionnaire items, we calculated the Cronbach alpha coefficient: dysphoria - 0.91; interference with activity - 0.84; body image - 0.58; health concern - 0.60; food avoidance - 0.81; social reaction - 0.71; sexual concern - 0.86; relationships - 0.76; and overall score - 0.9516 –showing a high internal consistency.

Results: A total number of 210 IBS patients - 146 (70%) females and 64 (30%) males - with ages between 18-75 years were assessed. In a comparative study regarding QOL in IBS vs. healthy subjects we found that food avoidance and emotional health concern are the most important subscales that affect the life quality in IBS patients ($p < 0.001$). The mean age of females and males was comparable (39.83 ± 12.50 vs. 39.87 ± 11.13 years, $p = 0.873$). No statistically significant difference ($p = 0.117$) between genders was noticed, albeit total symptom score was lower for females than males (54.86 ± 19.95 vs. 59.80 ± 18.79). Using the Chi-square Test for Independence we found that IBS women are more concerned with their body image than men ($p = 0.048$). Regarding the occupational status, IBS students (22.61 ± 2.57 years) were more affected than elderly subjects (59 ± 7.26 years) and retired patients with chronic comorbidities - 42.75 ± 18.84 vs. 62.15 ± 17.07 - $p < 0.01$.

A decreased QOL in IBS patients was noticed, similar to IBD patients. Albeit total symptom score was greater in IBS patients than IBD patients (56.36 ± 19.69 vs. 54.12 ± 22.24), no statistically significant difference ($p = 0.615$) was noticed. The lowest subscale score was for food avoidance (36.34% vs. 40.17%) and the highest subscale score was for body image (72.50% vs. 76.19%) in both groups.

Conclusion: IBS patients experience significant impairment in their QOL. In our study, the incidence of IBS was higher in females, with no differences in life quality among genders. Based on the occupational status, we noticed that IBS medical students are the most affected, stress having a major role in accentuating symptomatology. Quality of life in IBS patients is decreased, similar to IBD patients.

New onset of ascites after delivery as a first sign of recurrent colorectal cancer with peritoneal carcinomatosis in a young female patient

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Background: Colorectal cancer (CRC) is the third most common cancer in women, with the highest incidence in patients aged 50 years or older and 3% in patients younger than 40 years of age. The diagnosis of a CRC recurrence in pregnant women represents a challenge and is usually delayed, because of a significant overlap in signs and symptoms between a colorectal malignancy and normal pregnancy. Once diagnosis is made, further challenges exist, as treatment options may be limited. This was also the case of a patient with a recurrence of metastatic adenocarcinoma of the sigmoid colon during pregnancy, after four years of remission.

Case Presentation: A 26 year old female with no prior medical problems and a negative family history was diagnosed in a routine checkup with three solid liver masses with the appearance of liver metastases, which were confirmed by an abdominal CT scan. The histological analysis revealed metastases of an adenocarcinoma, which was endoscopically localized in the sigmoid colon. After three courses of neoadjuvant chemotherapy with FOLFOX/Cetuximab, a sigma resection and in-situ-split liver resection of the liver metastases was performed. Microsatellite analysis of the tumor tissue and germline testing for mismatch repair gene alterations in the genes MLH1, MLH2, MSH6 and PMS2 were negative, showing no evidence of hereditary non-polyposis colorectal cancer (HNPCC). Adjuvant chemotherapy with three courses of FOLFOX/Cetuximab was administered. The follow-up care showed a stable disease without signs of recurrence in the CT/MR scans for the next four years, including the follow-up

during the 2nd trimester of a planned pregnancy. After delivery, the patient noticed a persistently increased abdominal girth and difficulty in losing the pregnancy weight, so an MR scan was again performed. This showed a recurrence of the CRC with diffuse liver metastases, peritoneal carcinomatosis and ascites. The patient is now receiving a palliative chemotherapy with FOLFOX/Cetuximab.

Discussion: CRC is the seventh most common type of cancer in pregnancy with a reported incidence of 0.002%. While the overall incidence of CRC is steady or decreasing, some studies report an increased incidence of CRC in younger patients, even in the absence of HNPCC or familial adenomatous polyposis (FAP). Diagnosis of CRC in pregnant women is usually delayed, as abdominal symptoms are common in pregnancy and CRC can mimic them. Some data demonstrates that 20-54% of colon cancers have oestrogen receptors, whereas other demonstrates progesterone receptors, which may be stimulated by the oestrogen and progesterone produced during pregnancy. The role of these hormones in the etiology and progression of CRC, as well as CRC pathogenesis and its relation to pregnancy is not well understood, therefore further studies are required to evaluate a possible association between them.

Conclusions: CRC is an aggressive cancer that can also recur during pregnancy and is mostly diagnosed in late stages in this case. A thorough physical examination, laboratory evaluation and consideration of nonobstetric disease are important, especially if symptoms persist or increase in intensity, as an early diagnosis improves survival and treatment outcomes. An aggressive or recurrent course of disease can occur after years of stability even in young patients without HNPCC, FAP or family history, though the role of the pregnancy hormones in the pathogenesis of CRC is still to be understood.

Diagnostic accuracy and therapeutic efficacy of digital single-operator cholangioscopy for biliary lesions and stenosis

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Background & Aim: Digital single-operator cholangioscopy (dSOC) has revolutionized bile duct visualization during endoscopic retrograde cholangiography (ERC). Interventions like electrohydraulic or laser lithotripsy, inspection of suspicious areas and taking targeted biopsies have become possible quickly and easily. One main indication for dSOC remains the evaluation of indeterminate biliary strictures.

Patients and Methods: In this study, 180 dSOCs performed in 2016 till 2017 in a high volume tertiary center have been retrospectively analyzed to evaluate sensitivity, specificity, as well as positive and negative predictive values for indeterminate

strictures and lesions. Furthermore, technical success and complications were analyzed.

Results: In 92-97% of cases the region of interest was reached and visualized and in 83-100% successful biopsies were taken in the biliary tract in this study. Only the distal bile duct was less successful, with only 84% and 62%, respectively. The procedure was safe, with cholangitis as main complication. Regarding the diagnostic accuracy of dSOC for indeterminate biliary lesions and strictures, we found a sensitivity of 0.87 and specificity of 0.88. The investigators assessment directly after dSOC had a positive predictive value of 0.63 and a very high negative predictive value of 0.97.

Conclusions: Our study demonstrated that dSOC has a very high diagnostic efficacy, as well as a favorable safety profile. Therefore, it should be discussed as a standard of care in addition to ERC for indeterminate biliary lesions.

A case of cholangioscopy assisted stenting of the common bile duct

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Background: In the present days, cholangioscopy is being increasingly used for intraductal lithotripsy and targeted biopsies. We present a case of sepsis due to acute cholangitis that was successfully treated by using the cholangioscope for common bile duct guidewire catheterization proximal to the stenosis.

Case Report: A 75 years old patient with a history of iatrogenic stenosis of the common bile duct (CBD) (postcholecystectomy - 5 years ago) and ERCP complicated with perforation of the CBD treated conservatively (3 months prior to the last admission) presented in the emergency room for jaundice, fever, chills, sleeplessness and right upper abdominal quadrant pain. Clinical examination revealed: low blood pressure, tachycardia and disorientation. Biological findings: leukocytosis with neutrophilia, increased CRP and procalcitonin, hyperbilirubinemia, increased cholestasis enzymes. Ultrasound examination and CT-scan revealed dilatation of the proximal part of the CBD and intrahepatic bile ducts, and a tight area of stenosis on the medium part of the CBD. The previous ERCP (3 months before) intended for stenting the stenosis was unsuccessful and resulted in perforation of the CBD. The present diagnosis of sepsis secondary to acute cholangitis complicated with hypotension and acute renal failure indicated a new ERCP as the life-saving intervention. After repeatedly failing to catheterize with the guidewire and under X-ray the CBD proximal to the stenosis, we decided to use a cholangioscope to pass the guidewire. Cholangioscopy showed video images of the previous ERCP perforation site and the tight iatrogenic stenosis, which was then successfully passed with the guidewire and the stent was placed. Postprocedural outcome was favorable and the patient was discharged after 5 days.

Conclusion: Therapeutic cholangioscopy is used for visually guided treatment of difficult biliary stones by using intraductal lithotripsy, for ablation of biliary tumors and for facilitation of guidewire advancement into selective intrahepatic ducts for adequate biliary drainage. The case presented above reveals the latter, less common usage, that can become life-saving when radioscopically-assisted catheterization fails.

Intraductal Tubular Papillary Neoplasm (ITPN) – a new kid on the block of epithelial pancreatic neoplasms and precursor of pancreatic cancer

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Background: Intraductal tubular papillary neoplasm (ITPN) has been described for the first time by Yamaguchi et al. in 2009 and displays a very rare subtype of pancreatic neoplasms. According to the most recent WHO classification 2010, ITPNs are intraductal, grossly visible, tubule-forming epithelial neoplasms with high-grade dysplasia and ductal differentiation. In contrast to intraductal papillary mucinous neoplasm (IPMNs), no apparent epithelial mucin production is noted. Due to its rarity, clinical data about ITPN and pancreatic cancer arising in this tumor entity remains very limited.

Case presentation: A 68-year-old male with a distal bile duct occlusion due to a solid pancreatic head tumor underwent pylorus preserving duodenopancreatectomy at our institution. While preoperative staging was characteristic for a ductal adenocarcinoma of the pancreatic head or a distal bile duct cancer, final histopathology surprisingly revealed ITPN with an associated invasive carcinoma pT3, pN0 (0/12), R0, G2. The tumor had a diameter of 5.9 cm and showed wide infiltration of the duodenum. All resection margins were clear and 12 lymph nodes were free of tumor. According to a tumor board decision, the patient received adjuvant chemotherapy with Gemcitabine and Xeloda. To date, the patient is in a good clinical condition without signs of recurrent disease.

Discussion: ITPN is a rare entity of cystic pancreatic neoplasms. It has been estimated that ITPN accounts for less than 1% of all pancreatic exocrine neoplasms and for only 3% of all intraductal tumors. Since patients with ITPN commonly present with jaundice and a solid lesion of the pancreatic head suspicious for ductal adenocarcinoma, many tumors are not found before final histopathological examination. ITPN is frequently compared with IPMN. Both entities show growth within the pancreatic ducts and a relevant potential for malignant transformation. While IPMN is characterized by an excessive mucin production, ITPN does not show this attribute. Moreover, ITPN reveals a distinct tubule-forming epithelium on routine

hematoxylin eosin staining which is exclusively seen in this entity. While ITPNs most commonly arise in the main pancreatic duct, IPMN affects side branches in more than 80% of the cases. To further distinguish ITPN from IPMN, immunohistochemistry and molecular pathology can be helpful. Due to its malignant potential, radical oncologic resection is warranted for ITPN and, as far as it is known, displays the only curative treatment option.

Conclusion: ITPN displays a rare entity of pancreatic neoplasms with intraductal growth. As shown in the present case report, ITPN can be precursors for pancreatic cancer. Following radical surgical resection and adjuvant chemotherapy, prognosis is estimated to be more favorable when compared to regular ductal adenocarcinoma.

Intraoperative ultrasound (IOUS) of hepatobiliary tumors: clinical indications and application of US elastography and contrast-enhanced ultrasound (CEUS) during liver and pancreas tumor surgery

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Intraoperative ultrasound (IOUS) is routinely used during hepatobiliary operations. Current studies as well as own experiences proved that IOUS can optimize the detection and characterization of focal liver and pancreatic lesions compared to preoperative imaging diagnostics. Furthermore, the intrasurgical use of ultrasound elastography enables an improved marking of resection or ablations margins. In addition to routinely B-mode US, modern US techniques such as US elastography and contrast-enhanced ultrasound (CEUS) have become increasingly important: in comparison to B-mode US these techniques enable an even more accurate detection, visualization, differentiation and characterization of focal liver or pancreatic lesions, so that ablation or resection margins can be immediately adapted individually for each patient during surgery. Thereby, the patients' outcome can be improved, though experience in elastography and CEUS application is needed.

Response of liver and spleen stiffness to portal pressure lowering drugs in a rat model of cirrhosis

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Background & Aim: Liver stiffness (LS) is increasingly used to screen for liver fibrosis. In addition, spleen stiffness (SS) is an established parameter to assess portal hypertension, which is tightly related to the hemodynamics of blood flow and vascular resistance. Little is known about the response of LS and SS to vasoactive substances. We here studied LS and SS in a Thioacetamide (TAA)-induced cirrhosis rat model after exposure to various vasoactive drugs using a miniaturized Fibroscan platform (μ Fibroscan).

Methods: We induced cirrhosis in 24 wildt-type 8 weeks old adult male Wistar rats with 200 mg/Kg dosage of Thioacetamide (TAA) through intraperitoneal injection of 50 mg/ml solution 2 times per week for 6 weeks. The six groups consisted of control (sodium chloride), metoprolol, udenafil, enalapril, terlipressin and carvedilol. LS and SS were measured by μ Fibroscan (Echosens, Paris). The rats underwent general anesthesia with isoflurane inhalation. After anesthesia, abdominal aorta, inferior vena cava and portal vein were cannulated with 24-gauge cannula and connected to Power lab device (AD instruments) to continuously measure the mean arterial pressure (MAP), heart rate (HR) and portal vein pressure (PVP). Drugs were injected systemically and data were collected at time points 0, 15 and 30 minutes.

Results: LS and SS were significantly higher in TAA treated rats than in the control group (23.8 vs 3.8 kPa and 19.6 vs 47.8 kPa, $P < 0.0001$). In addition, they had significantly bigger and heavier spleens (6 vs 4 cm and 2.7 vs 1 g, $P < 0.0001$, respectively). After application of all drugs, LS and SS followed tightly the change of the portal vein pressure ($r = 0.681$ and 0.622 , $P < 0.01$, respectively). Also, SS was significantly correlated with the spleen size and weight ($r = 0.723$ and 0.663 , respectively < 0.01). Noteworthy, a significant decrease of PVP ranging from 22% to 34% ($P < 0.05$) was observed after 15 to 30 minutes with metoprolol, udenafil, enalapril and carvedilol, which was accompanied by a significant decrease in LS and SS ranging from 18.2 to 44% ($P < 0.05$) (Table I). Interestingly, after terlipressin, LS and SS only slightly decreased, which could be explained by counteracting PVP and MAP. Thus, while PVP decreased by 20% ($P < 0.001$), MAP increased by 35% ($P < 0.001$). Overall, carvedilol showed the best response regarding the decrease of PVP, LS and SS. Of note, the heart rate increased

after metoprolol and udenafil injection (ca. 10%, $P < 0.05$), while it decreased in response to terlipressin and carvedilol by cca 30% ($P < 0.01$).

Conclusion: In our study, LS and SS strongly correlated with PVP and responded differently to various vasoactive drugs. Combined non-invasive LS and SS measurement could be useful to monitor the patient's response and compliance to portal pressure lowering drugs.

Feasibility of transient elastography for the evaluation of liver fibrosis in patients with type 2 diabetes mellitus

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Aim: The aim of this study was to evaluate the feasibility of Transient Elastography (TE) for the evaluation of liver fibrosis in patients with type 2 Diabetes Mellitus (T2DM).

Material and Method: We prospectively included 692 patients with T2DM displaying no known liver disease, in which liver fibrosis and steatosis was evaluated by means of TE and Controlled Attenuation Parameter (CAP). All patients enrolled in this study were under fasting condition. We used the following cut-offs for quantification of liver steatosis by means of CAP: 250, 270, 290 for mild, moderate and severe steatosis (S1, S2, S3, respectively) [1]. For differentiation between stages of liver fibrosis, the following cut-off values were used: $F2 \geq 7$ kPa, $F4 \geq 10.3$ kPa [2].

Results: Mean of age of the study population was 60 ± 10.2 y, 54% female and mean BMI was 31.7 ± 6 . Reliable elastographic measurements were obtained in 78.9% (546/692) patients. The remaining 546 patients were used for further statistical analysis. By using the proposed cut-off values, significant fibrosis (F2-F3) was found in 22% (120) patients with T2DM, while 18.9% (103) had cirrhosis (F4). The prevalence of liver steatosis was the following: S0 – 14.2% (78), S1 – 8.85 (48), S2 – 11.3% (61), S3 – 65.7% (359).

Conclusion: TE shows good feasibility for evaluating liver fibrosis in patients with T2DM. Liver steatosis is frequently found in T2DM patients, while a significant liver stiffness increase was found in almost 40% of these patients. Liver stiffness assessment in type 2 diabetic patients should be routinely performed to identify those with significant liver fibrosis.

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Table I. Influence of vasoactive drugs on liver stiffness (LS) and spleen stiffness (SS)

Drug/ Parameter	Delta LS (P Value)	Delta SS (P Value)	Delta PVP (P Value)	Delta MAP (P Value)	Delta HR (P Value)
Metoprolol	-19% (< 0.05)	-21.9% (< 0.001)	-22% (< 0.001)	-20.1% (< 0.01)	+7.5% (< 0.01)
Udenafil	-18.2% (< 0.05)	-27.7% (< 0.001)	-26.2% (< 0.001)	-16.5% (< 0.05)	+7.9% (0.105)
Enalapril	-34% (< 0.05)	-22.3% (< 0.001)	-25.4% (< 0.001)	-13.5% (< 0.01)	-0.3% (=0.125)
Terlipressin	-3.7% (=0.08)	-15.8% (=0.19)	-20.1% (< 0.001)	+35.2% (< 0.01)	-27.6% (< 0.01)
Carvedilol	-44.6% (< 0.05)	-29.7% (< 0.001)	-33.1% (< 0.001)	-35.8% (< 0.05)	-42.1% (< 0.01)

Intra- and interoperator reproducibility of a time harmonic elastography and the impact of ultrasound experience in achieving reliable results

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Aim: The aim of this study was to evaluate the inter- and intraobserver reproducibility of the new time-harmonic elastography diagnostic system (THED) [1] and the impact of ultrasound (US) experience in acquiring reliable measurements, as no official recommendations are available for this system.

Material and Methods: Elastographic measurements (EM) were obtained in 27 consecutive subjects using THED. Three examiners with different levels of experience in US and US-based elastography performed 10 valid EMs on each subject. We defined their experience as follows: E1: no experience in elastography and less than 50 US examinations; E2: more than one year elastographic experience and more than 500 US examinations, and E3: more than 1000 US examinations, without any experience in elastography. We used the intraclass correlation coefficient (ICC), inter-rater agreement (Kappa coefficient) and concordance correlation coefficient to assess the inter- and intraobserver reproducibility.

Results: We did not find significant differences between the means of EM obtained by the examiners overall and across study group [1.66 (E1) vs 1.66 (E2) vs 1.65 (E3), $p=0.76$]. The overall agreement between examiners was excellent: 0.94 (95% CI: 0.89-0.97). There was at least a good agreement between examiners (E1 vs. E3: $k=0.80$, 95% CI: 0.67-0.94; E1 vs. E2: $k=0.81$, 95% CI: 0.69-0.94), and good to excellent in E2 vs. E3: $k=0.89$, 95% CI: 0.82-0.96. The intraobserver reproducibility for each of the examiners was excellent, however the ICCs were higher in more experienced examiners in US: E1-0.92, (95% CI: 0.82-0.96) vs. E3-0.94 (95% CI: 0.87-0.97) vs. E2-0.97 (95% CI: 0.95-0.99). The concordance correlation coefficients were similar: E1 vs. E3-0.84, E1 vs. E2-0.89 and E3 vs. E2-0.89.

Conclusions: The good ICCs and Kappa coefficients for the mean values show that THED is a reproducible method. Ultrasound experience did not significantly influence the results.

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How many patients with metabolic syndrome have liver fibrosis and steatosis?

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Background & Aim: Patients with metabolic syndrome have many patients liver steatosis (NAFLD) and sometimes this can be followed by significant liver fibrosis. The aim of the present study was to determine the severity of liver steatosis and fibrosis in a cohort of patients with metabolic syndrome, using non-invasive methods: Transient Elastography (TE) with Controlled Attenuation Parameter (CAP) and ultrasound.

Material and Methods: 55 patients with metabolic syndrome were prospectively enrolled. Liver fibrosis and steatosis were evaluated using Transient Elastography (FibroScan) with Controlled Attenuation Parameter (CAP), performed in fasting conditions, using both M and XL probes. Reliable liver stiffness measurements (LSMs) were defined as the median value of 10 LSM with an IQR/median <30%. Steatosis was evaluated by means of ultrasound and graded in mild, moderate and severe. A semi-quantitative scale was used, according to the subjective assessment of the "brightness" of the liver as compared to the renal parenchyma and the intensity of "posterior attenuation". When the evaluation of steatosis was performed by CAP we used the following cut-off values proposed by the manufacturer: S1 (mild) <230, S2 (moderate): 275-300 db/m, S3 (severe) > 300 db/m. On the other hand, a cut-off value of 8.5 kPa [1] was used to define clinically relevant fibrosis ($F\geq 2$).

Results: Reliable LSMs were obtained with FibroScan in 94.6% (52/55) of the patients. The mean age of these patients was 59.4 ± 10.5 , the majority of them were males (60%) and the BMI was $35.1\pm 5.02\text{kg/m}^2$. Moderate and severe steatosis evaluated by means of CAP was found in 7.7% and 75% cases, respectively. Clinically relevant fibrosis was detected by means of TE ($\text{LSM}\geq 8.5\text{ kPa}$) in 25% (13/52) of subjects, all subjects concomitantly had CAP values $\geq 300\text{db/m}$, suggesting severe steatosis. The correlation between CAP and ultrasound assessment of steatosis was strong ($r=0.90$, $p<0.0001$).

Conclusions: In our study group, 82.7% of patients with metabolic syndrome had moderate and severe steatosis by CAP and 25% of them had clinically relevant fibrosis by TE. Standard ultrasound of the liver showed a good correlation with CAP for the evaluation of steatosis.

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Hepatic overexpression of chemerin attenuates inflammation and fibrosis in murine non-alcoholic steatohepatitis

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Background & Aim: Non-alcoholic liver disease (NAFLD) is one of the main rising chronic diseases in the western affluent society. The pathophysiology of NAFLD is closely linked to obesity and mainly results from excessive triglyceride storage in the liver. Inflammation of the fatty liver is the hallmark of non-alcoholic steatohepatitis (NASH), a progressive form of NAFLD, with very limited pharmacological therapy options to date. The chemokine chemerin is mainly expressed in hepatocytes and adipocytes. In human NAFLD, chemerin mRNA levels are negatively associated with hepatic fibrosis and inflammation scores. Aim of this study was to investigate the potential hepatoprotective properties of hepatic chemerin-overexpression in a rodent NASH-model.

Methods: Eight-week old C57BL/6J mice were intraperitoneally injected with adeno associated virus 8 (AAV8) with a chimeric promoter to achieve liver-specific expression of the full-length chemerin protein. As controls, C57BL/6J mice were injected with AAV8 virus containing the empty transfer vector. Steatohepatitis was induced by feeding a methionine- and choline-deficient diet for two weeks. Hepatic mRNA and protein expression of inflammatory and fibrotic markers were analyzed by qRT-PCR and western blotting, respectively. Systemic chemerin, adiponectin, glucose and insulin levels and hepatic triglyceride content were determined by ELISA and colorimetric assays.

Results: Hepatic and systemic chemerin levels increased more than twofold in comparison to control animals, suggesting that protein produced in the liver contributes to circulating levels. Hepatic triglyceride concentrations were not changed by this intervention. The hepatic mRNA expression levels of inflammatory markers such as tumor necrosis factor alpha or F4/80 were significantly reduced in chemerin-overexpressing mice compared to the control group. Furthermore, hepatic mRNA expression of fibrotic marker genes such as transforming growth factor beta and alpha smooth muscle actin was significantly decreased in chemerin overexpressing mice. No differences between the two experimental groups were observed for systemic levels of insulin, glucose or the hepatoprotective adipokine adiponectin.

Conclusion: Our study demonstrates the anti-inflammatory and hepatoprotective effects of chemerin.

Color coded perfusion imaging with contrast enhanced ultrasound (CEUS) for post-interventional success control following

irreversible electroporation (IRE) of liver lesions

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Aim: Evaluation of the post-interventional success following irreversible electroporation (IRE) using a new color coded perfusion quantification software with CEUS in patients with hepatocellular carcinoma (HCC).

Material and Methods: 38 patients (9 females, 29 males, age range 46 – 82 years, mean 59.5 years) with 65 malignant liver lesions underwent IRE between 01/2013 and 12/2017. All patients were examined with CEUS using a linear multifrequency probe (1-5 MHz) within 24 hours following IRE to detect residual tumor tissue. A retrospective evaluation using a perfusion quantification software regarding peak enhancement (pE), time-to-peak (TTP), mean transit time (mTT), rise time (Ri) and wash-in area under the curve (WiAUC) in the center of the lesion, the margin and surrounding liver was performed.

Results: In all lesions, a post-interventional reduction of the tumor microvascularization was found. For WiAUC and pE the differences between center of the lesion vs. margin were found to be statistically significant ($p < 0.01$ - pE and $p < 0.001$ WiAUC). Differences between the lesion and surrounding tissue were also statistically significant for WiAUC ($p < 0.05$). mTT, TTP and Ri showed no significant difference between center, margin or surrounding tissue.

Conclusion: CEUS with perfusion imaging is a valuable supporting tool for post-interventional success control following IRE of liver lesions. Peak enhancement and WiAUC seem to be the most valuable parameters.

A 19 year-old patient with severe Budd-Chiari syndrome rescued by emergency TIPS placement

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Case Presentation: A 19-year-old female patient was transferred to our intensive care unit with ascites, abdominal tension, nausea and gain of weight of 1.5kg within one week. The patient has been diagnosed with a classified low risk - essential thrombocythemia (ET) harbouring JAK2-V617F-Mutation.

Initial blood tests showed a lowered blood clotting (Quick 70%), low factor 5 activity (69%) as well as elevated liver enzyme activities (GOT 300 U/l, GPT 400 U/l). CT imaging

revealed a Budd-Chiari syndrome with hepatomegaly and an inhomogeneous contrasting of the liver. Both right hepatic vein and middle hepatic vein were not demarcated. The patient was admitted to our ICU and anticoagulation was initiated. Since ascites and liver enzymes activity increased over the following 3 days and liver function deteriorated, we decided for vascular interventions. The intervention showed a hepatic venous pressure gradient (HVPG) of 18mmHg. Thus, we placed TIPS. After that, HVPG was 7 mmHg.

With the occurrence of venous embolism the ET was upgraded to a high risk ET. Hence, cytoreductive therapy was initiated. Therefore, we administered hydroxyurea with the goal of a platelet count <350 cells/nl. Furthermore, we administered clopidogrel as antiplatelet agent.

Conclusion: We presented the case of a 19-year-old patient who initially presented with abdominal pain and elevated liver enzymes at our emergency department. CT imaging showed a severe Budd-Chiari syndrome. The patient could be rescued by emergency TIPS placement and was discharged from hospital in excellent general condition with completely recovered liver function. The rationale behind TIPS placement in Budd-Chiari syndrome is to decompress congested segments of the liver by establishing an alternative venous outflow tract. However, TIPS placement is technically demanding in Budd-Chiari syndrome and if not successful, liver transplantation is the only option.

TIPS placed before current hospitalization and early admission to ICU increase survival of patients with cirrhosis and sepsis

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Background & Aim: In times of decreasing numbers of organ donors, more and more patients with cirrhosis of the liver with high MELD-Score are hospitalized at intensive care units (ICUs). Patients with cirrhosis are immunocompromised and infections are a common clinical problem. This study analyzes the impact of infections and sepsis on patients with cirrhosis.

Methods: In a retrospective analysis, 157 patients with cirrhosis hospitalized in 2017 at an ICU with a focus on hepatology were analyzed for the incidence of sepsis. Furthermore, cause of sepsis, influencing factors and outcome were examined.

Results: 131 of 157 patients (83%) with cirrhosis were diagnosed with sepsis according to Sepsis-3 criteria. Most common causes for sepsis were pneumonia, urinary tract infection and spontaneous bacterial peritonitis. Pathogen detection was successful in 76% of patients with sepsis. Most frequently enterococci and gram-negative bacteria could be identified. Average length of the duration of stay of patients with cirrhosis and sepsis at ICU was 13.2 days, which is clearly prolonged in comparison to the length of stay of patients with cirrhosis without sepsis (3.0 days). ICU survival of patients with

cirrhosis and sepsis was 68%. Survival was significantly better (85%) when patients were admitted directly to ICU from the emergency department and, thus, received specialized intensive care treatment ab initio. Remarkably, patients with transjugular intrahepatic portosystemic shunt (TIPS) placed before current hospitalization had an excellent ICU survival (92%).

Conclusions: The study shows that sepsis is a very common cause for admission to ICU for patients with cirrhosis. Furthermore, the study underlines that an early specialized intensive care treatment improves survival for patient with cirrhosis and sepsis. Patients with TIPS placed before current hospitalization had an excellent ICU survival, most likely due to a reduced bacterial translocation from the gastrointestinal tract because of a reduced portal venous pressure. This further supports current data that TIPS increases transplant-free survival of patients with cirrhosis.

The role of TIPS in the management of patients with liver cirrhosis – experience of a tertiary center

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Background & Aim: Transjugular intrahepatic portosystemic shunt (TIPS) implantation is used for treatment of several complications in patients with liver cirrhosis. Recent studies have identified a clinical and survival benefit for patients with liver cirrhosis. In this study, we analyzed the clinical course of patients after TIPS implantation.

Methods: In this retrospective analysis, 73 patients (19 female, 54 male) were followed up for an interval of 12 months after TIPS implantation. Data acquisition comprised the time period January 2016 until July 2018. All patients were examined at 3 months after the procedure, then after 6 months and 12 months. At each visit, liver disease-related complications, treatment modifications, and clinical and biochemical variables needed to calculate Child-Pugh and Model for End-Stage Liver Disease scores were recorded.

Results: The average age of the patients was 55.75 years (± 11.12 SD) and the etiology of the liver disease was ethyl-toxic (68%), NASH (8%), hepatitis B/C infection (8%), Budd-Chiari syndrome (5.3%) and cryptogenic (10.7%). The majority of the patients suffered from an advanced liver disease (Child-Pugh stadium B/C = 91.7%).

Direct and peri- or post-interventional complications, all manageable, occurred in 9.7% of the patients. TIPS implantation had a positive influence on liver function (MELD Score d1: 13.38 mean; month 12: 12.17). Furthermore, we observed an improvement of liver related blood test values, such as transaminases and albumin, while a discrete impairment of bilirubin occurred. The use of diuretics decreased over the study period.

Conclusion: TIPS implantation is a safe procedure even in patients with advanced liver cirrhosis. Therefore, TIPS should be considered at an early stage in the management of patients with liver cirrhosis.

Mucus impairment drives direct bacteria to cell interaction and promotes bacterial translocation in liver cirrhosis

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Background & Aim: Patients suffering from liver cirrhosis display impaired intestinal characteristics compared to healthy individuals, indicated by a suppressed immune system, bacterial overgrowth, reduced microbial diversity and - of special importance - an increased permeability of the intestinal epithelial barrier. Together, these changes promote bacterial translocation, driving spontaneous bacterial peritonitis (SBP), one of the most harmful complications of liver cirrhosis. So far, molecular mechanisms explaining bacterial translocation have not been elucidated. Thus, the aim of this study was to characterize intestinal properties in colonic biopsies from liver cirrhosis patients and furthermore to simulate interactions of bacteria with intestinal epithelial cells in an in vitro model.

Methods: In vitro, Caco-2 human intestinal epithelial cells were cocultured with *Escherichia coli* (*E. coli*) for 4 hours. *E. coli* LPS and supernatant of *E. coli* overnight cultures were used for stimulation also. Effects on cell-cell-contact proteins (occludin, E-cadherin) were studied by Western blot. Transwell experiments were performed to evaluate the impact of direct bacteria-cell-interaction. Intestinal biopsies of 20 controls and 8 liver cirrhosis patients (4x child-pugh A, 4x child-pugh C) were included in the study. For analysis of the mucus layer, frozen sections of intestinal biopsies were stained with alcian blue. Protein levels of occludin and E-cadherin were analyzed by immunohistochemistry.

Results: Up to 50% reduced protein levels of occludin and E-cadherin were observed upon bacterial stimulation of Caco-2 cells. This destabilization of the epithelial barrier required a direct interaction of Caco-2 cells and bacteria. In contrast to living bacteria, *E. coli* supernatant reduced E-cadherin and occludin levels by only 30% and LPS failed to induce any changes. In accordance with these in vitro data, occludin and E-cadherin levels in intestinal biopsies of liver cirrhosis patients decreased with the onset of a SBP. Remarkably, the mucus layer of liver cirrhosis patients (12.8 µm) was strongly reduced compared to controls (16.4 µm).

Conclusion: Gram-negative bacteria such as *E. coli* are able to impair the integrity of the epithelial barrier. This effect requires a direct interaction of bacteria with intestinal epithelial cells. The diminished mucus layer seen in liver cirrhosis patients

facilitates such a direct interaction, which further destabilizes the epithelial integrity and promotes bacterial translocation.

Antisense oligonucleotide targeting TGFβ-signalling prevents fibrosis in LX-2 cells

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Background & Aim: Liver fibrosis is characterized by production of extracellular matrix (ECM) by hepatic stellate cells. This promotes cirrhosis and hepatocellular carcinoma (HCC). The multifunctional cytokine TGFβ is a key player in development of liver cirrhosis and HCC. Therefore, targeting TGFβ signalling would be an integral therapeutic approach to influence both, fibrosis and its complications. In this study we present the effects of an antisense oligonucleotide (ASO) on LX-2 cells in vitro.

Material and Methods: Immortalised human hepatic stellate cells (LX-2 cell line) were stimulated with 10 ng/ml TGFβ. ASO-induced knockdown of the TGFβ RII was performed; control was done by a scrambled ASO. RT-PCR was performed to measure the knockdown of TGFβ RII and the expression of ECM components. Effects on protein level were visualised via fluorescence microscopy and quantified via protein assay.

Results: AOS reduced the expression of TGFβRII mRNA to an extent of 80% after 48 h in the presence and absence of TGFβ. After stimulation of LX-2 cells with TGFβ the HSC activation marker CTGF and the expression of the ECM components ACTA2, collagen I and fibronectin were significantly reduced by the ASO, but not by the control on transcriptional level. Fluorescence microscopy showed that transformation of LX-2 cells to a myofibroblast-like phenotype was altered by the ASO. Expression of TGFβRII and ECM components were reduced by the ASO, but not by the control. ELISA revealed a ASO-mediated reduction of TGFβ-induced proinflammatory cytokines in the supernatant of stimulated cells.

Conclusion: An ASO against TGFβ RII reduced profibrotic factors on transcriptional and protein level in LX-2 cells and showed anti-inflammatory effects in vitro. Therefore, this ASO could be a potential therapeutic approach to reduce fibrosis and progression of cirrhosis.

Diagnosis of spontaneous bacterial peritonitis using innovative biomarkers from ascitic samples

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Background & Aim: With a one-year mortality of up to 70%, spontaneous bacterial peritonitis (SBP) is a severe complication in decompensated liver cirrhosis. It is defined as bacterial infection of the ascitic fluid without any intra-abdominal surgically treatable focus. Although the pathogenesis of this disease is not yet fully understood, bacterial translocation of intestinal bacteria from the gut to mesenteric lymph nodes and into ascitic fluid is regarded as the major underlying process. According to the German S3-Guideline “Ascites, spontaneous bacterial peritonitis, hepatorenal syndrome”, SBP diagnosis is assured with the detection of >250 polymorphonuclear (PMN) cells per μl . Since antibiotic treatment is indicated at the very onset of SBP, innovative potential biomarkers for early SBP diagnosis are in great demand.

Methods: To identify novel potential biomarkers for SBP, ascitic fluid was collected from patients suffering liver cirrhosis at the University Hospital of Regensburg. Protein levels of lactoferrin, C3a, IP-10, IL-6, IL-8 and IL-10 within ascitic fluids were determined by ELISA. Total protein content of ascitic fluid was measured by BCA protein assays.

Results: In total, 69 ascitic fluid samples from 41 individual patients were analyzed. The age of the patients was 36 - 77 years at the moment of paracentesis. 32 patients (78%) were male and 9 patients (22%) were female. Etiology of liver cirrhosis was alcohol-toxic (58.5%), cryptogenic (19.5%), nutritional-toxic (7.3%), viral (4.9%), autoimmune (2.4%), PBC (2.4%), non-alcoholic steatohepatitis (2.4%) and Budd Chiari Syndrome (2.4%). In 11.6 % (8) of the samples, diagnosis of SBP was confirmed by detection of > 250 PMN/ μl . However, using a PMN cell count of more than 100 PMN/ μl in the ascitic fluid detected SBP in 13 samples (18.8%). Lactoferrin levels in ascitic fluid of SBP samples (mean 1006 ng/ml) were higher than in ascitic fluid without SBP (mean 75ng/ml). Follow-up samples indicated that lactoferrin concentrations were elevated in the early stages of SBP and coincided with the course of the disease and therapeutic response. C3a levels also correlated with the course of disease, but were reduced in the infected ascitic fluid (mean 511ng/ml) compared to non-SBP samples (mean 975 ng/ml). IP-10 was detected in all samples, but did not display any correlation with disease activity. Also relevant amounts of cytokines IL-6, IL-8 and IL-10 were detected in the ascitic fluid of liver cirrhosis patients. However, an association of these parameters with the early onset of SBP was not observed.

Conclusion: Lactoferrin and C3a levels in the ascitic fluid of liver cirrhosis patients correlated with the onset and course of SBP. Strikingly, a lower PMN-cutoff resulted in an enhanced specificity for SBP. High levels of other inflammatory molecules and cytokines detected in ascitic samples highlight the tremendous inflammatory activity in ascitic fluids of liver cirrhosis patients. Thus, these results show SBP in a novel perspective and provide options for earlier diagnosis and treatment of the disease.

Reduction of p53 family members and induction of cell death by *E.coli* in intestinal epithelial cells - a mechanism of pathogenesis of spontaneous bacterial peritonitis

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Background & Aim: Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid without a detectable source of infection and is one of the most common complications in liver cirrhosis, with a very high 1-year-mortality of up to 93%. Until today, distinct mechanisms regarding the pathogenesis of SBP remain unclear, although it is assumed that bacteria translocate from the intestine into the ascites. The p53 family is known for its tumor-suppressive functions, but also has an impact on bacterial infections, e.g. by inhibiting inflammatory responses. To investigate how intestinal epithelial cells and bacteria interact, p53 and p73 regulation and induction of cell death of intestinal epithelial cells were examined upon bacterial stimulation.

Methods: The human intestinal epithelial cell line HCT-116wt expressing wildtype p53 and p73 was co-incubated with *Escherichia coli* (*E.coli*) at MOI0 to MOI5 for 2 or 4 hours. To compare effects of bacterial metabolites, cells were separated from bacteria by a semi-permeable membrane in a transwell approach. Protein levels of p53 family members were analyzed by Western blot. Cell death was analyzed by flow cytometry after co-incubation with *E.coli*, bacterial supernatant or supernatant of cells that were pretreated with bacteria. Moreover, cells were pretreated with different inhibitors of cell death (zVAD-FMK, Necrostatin-1, Ferrostatin-1), antioxidants (Trolox, NAC), an inhibitor of Cyclophilin (Ciclosporin A) and metal chelators (BAPTA-AM, 2,2'-Bipyridyl) to identify the type of cell death.

Results: Co-incubation of HCT-116wt and *E.coli* resulted in a decrease of p53 and p73 protein levels in a time- and dose-dependent manner. In contrast, p53 and p73 levels were unaffected when cells were separated from bacteria by a semi-permeable membrane or after co-incubation with heat-inactivated bacteria. Despite reduced p53 levels, co-incubation with *E.coli* induced high rates of cell death. Stimulation with supernatants of *E.coli*-pretreated HCT-116wt cells also resulted in increased cell death, albeit to a lower extent. In contrast, bacterial supernatants and heat-inactivated bacteria had no effect on cell survival. Cell death could not be blocked by zVAD-FMK, Necrostatin-1, Ferrostatin-1, Trolox, NAC, Ciclosporin A or BAPTA-AM. However, the iron chelator 2,2'-Bipyridyl significantly reduced cell death rates (84% vs. 59%).

Conclusions: Direct contact of intestinal epithelial cells with living bacteria resulted in downregulation of p53 family

members. Interestingly, despite the reduced levels of p53, E.coli caused cell death in HCT-116wt. This cell death was non-apoptotic, but might have been iron-dependent. As bacterial supernatants did not increase cell death, this leads to the suggestion that after the contact between bacteria and cells, either E.coli or HCT-116wt themselves produce soluble substances that initiate cell death. In the setting of liver cirrhosis, both effects might be part of a bacterial mechanism to protect themselves from host immune response and thus to overcome the intestinal barrier and cause SBP.

Partial spleen embolization in patients with liver cirrhosis - our preliminary experience

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Background & Aims: Thrombocytopenia due to hypersplenism is one of the most frequent consequences of portal hypertension in patients with advanced chronic liver disease (ACLD). Partial splenic embolization (PSE) is an effective durable treatment for severe thrombocytopenia in such patients, but it has been related to numerous adverse events. This procedure has been applied in our institution since 2017. The aim of this work was to analyze the benefits and safety regarding PSE for the treatment of thrombocytopenia in ACLD patients admitted to our institution.

Methods: Between November 2017 and January 2019, PSE was carried out in 15 patients with ACLD and thrombocytopenia (platelets level < 70.000/cmc). Clinical and biological changes up to 3 months post PSE were analyzed retrospectively. In 5 patients, data regarding hepatic venous pressure gradient (HVPG) and liver stiffness measurement (LSM) assessed with transient elastography performed before and 2-3 months after PSE was available.

Results: Indications for PSE were hepatocellular carcinoma awaiting for curative therapy (6 patients), indication for surgery other than for liver disease (1 patient), continuation of chemotherapy (1 patient), severe leucopenia and thrombocytopenia (4 cases) and severe thrombocytopenia alone (2 cases). The most frequent etiologies of ACLD were alcohol liver disease and hepatitis C related liver disease. Seven patients belonged to Child Pugh A and 8 patients to Child Pugh B class. There was a marked improvement of platelet levels after PSE (mean platelet level before PSE= 46,000/cmc and post PSE = 168,200/cmc). In 4 patients, thrombocytopenia was not compensated, however platelet levels rose above 60,000/cmc post PSE. All patients experienced minor adverse effects (pain in left upper quadrant, fever). The most frequent severe complication was spontaneous bacterial peritonitis (SBP) developed within 14 days post PSE in 7 patients (46.6%). Other complications were: portal vein thrombosis (4 patients

– 26.6%), splenic vein thrombosis (6 patients – 40%), superior and inferior mesenteric vein thrombosis (1 patient – 6.6%), transjugular intrahepatic portosystemic shunt dysfunction with subsequent variceal hemorrhage (1 patient), pleural effusion (6 patients - 40%), pneumonia (1 patient - 6.6%), subcapsular splenic collection (1 patient - 6.6%). Overall, only 3 patients (20%) were spared from any severe adverse events. Two patients died (death related to SBP and to extended superior mesenteric vein thrombosis, respectively, with a mortality rate of 13.3%). There was a slight decrease in HVPG and LSM after the procedure (mean HVPG value pre PSE = 15.7 mmHg vs. post PSE = 12.5 mmHg; r mean LSM value pre PSE = 28.15 kPa vs. post PSE = 22.27 kPa).

Conclusion: In our experience, PSE showed efficacy for the cure of severe thrombocytopenia. More than half of the patients experienced serious adverse events such as SPB and portal vein thrombosis. PSE might have an impact on portal hypertension in selected patients, for whom further studies should be performed, although the risks of developing complications overcome the benefits of the procedure.

Liver perfusion in critically ill patients with severe liver disease – Is there a correlation with outcome?

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Background & Aim: One of the major causes of morbidity and mortality worldwide are chronic liver diseases. Ultrasound examinations are very important for the evaluation of liver diseases, especially for critically ill patients hospitalized at intensive care unit. However the role of a routine Doppler sonography of liver perfusion in these patients was never examined. Therefore the aim of the study was to determine a potential correlation of liver perfusion with clinical outcome.

Methods: 50 patients with severe liver disease hospitalized at the intensive care unit of the Department of Internal Medicine I of the University Hospital Regensburg were routinely examined with sonography twice a week and liver perfusion was quantified by hepatic artery resistance index (HARI). MELD (Model for End-Stage Liver Disease) score was calculated for each patient.

Results: Statistic analysis showed a linear, positive correlation between HARI and MELD score. Initial regression analyses quantify these correlations with a R²-value of 0.220 (HARI – MELD score). HARI increased in patients who died during inpatient treatment on average by 1.6% with each examination, whereas it declined by 0.3% in non-deceased patients.

Conclusion: Our study shows, given the statistically significant correlation of HARI with the MELD score, that

liver perfusion is a prognostic factor for survival of patients with severe liver disease.

Influence of pre-transplant infections on the outcome of liver transplantation, a single center study

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Background & Aim: Organ allocation for liver transplantation (LTPL) in Germany follows the principle “sickest first”. Therefore, only patients with high MELD score-levels are undergoing liver transplantation and mortality of patients on the waiting list is high. High-MELD patients are especially at risk of infections. However, patients can be transplanted when infection is controlled at time of transplantation. Aim of this study was to define the influence of pre-transplant infections on the outcome post LTPL.

Methods: Clinical and laboratory characteristics of 84 patients that were transplanted in the University Hospital Regensburg from January 2014 to January 2018 were analysed in a retrospective single-center study.

Results: 38 (46.3%) out of 84 transplanted patients had infections during hospitalisation before transplantation. These infections were controlled at time of transplantation. Main causes of infections were pneumonia 52% (n=20) and SBP 13% (n=5); 40.5% (n=28) of patients with infections were septic. In 86% (n=33) of patients with infections the causing pathogens were identified, being enterococci (57,9% of patients with infections, n=22) staphylococci (52%, n=20), candida (47,3%, n=18), E.coli (31,5%, n=12) and klebsiellae (18,4% , n=7). Patients with pre-transplant infections had higher MELD scores at time of transplantation than those without infection (MELD 32 vs. MELD 18, p=0.001). Patients with pre-transplant infections had a longer stay on ICU post-transplantation (31 d vs. 14 d, p=0.002) and the total time of hospitalisation after LTPL was longer, but did not reach significance (69 d vs. 47 d, p=0.072). However, 90-day mortality did not differ (n=4 vs. n=3, p=0.69).

Conclusion: Infections before LTPL are mostly pneumoniae and occur in patients with high MELD scores. If these infections are controlled, LTPL can be performed. Pre-transplant infections do influence duration of ICU treatment post-LTPL, but do not affect 90-day mortality.

A simple clinical score to predict survival in patients with hepatocellular carcinoma

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Background & Aim: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third cause of death due to cancer. To date, the Barcelona Clinic Liver Cancer (BCLC) system is the most commonly used system for staging and prognosis of HCC. We aimed to create a simple score to predict survival in patients with HCC.

Methods: We retrospectively analysed data of the subsequent patients of mostly Caucasian descent, treated in the University Hospital Würzburg from 2005 to 2014 with proven HCC. We assessed the effect of different clinical and laboratory parameters at baseline on survival and included all statistically significant parameters in a Cox-regression model adjusted for prognostic factors like BCLC, Child-Pugh stage or age at diagnosis. Based on the remaining significant factors and odds ratios for survival, a clinical score was created (GOT (>50 U/l; 1.5 points), INR (>1.5; 2 points), platelet count (> 300,000/μl; 3 points), and presence of cirrhosis (2 points) and survival was calculated for the different values. Results were validated in another cohort of HCC patients (University Hospital Vienna). For the Würzburg cohort we did a separate survival analysis for platelet count only.

Results: 299 HCC patients (mean age 66.0 years) were included. 83.3% were male, 72.2% had a proven diagnosis of liver cirrhosis. BCLC stages ranged from 0 to D (0: 3.7%, A: 25.8%, B: 40.5%, C: 24.1%, and D: 5.7%). Metastasis and portal vein invasion were observed in 19.7% of the patients. Treatment of HCC generally followed the BCLC algorithm (resection 27.8%, RFA 7.0%, transplantation 4.7%, TACE 49.2%, SIRT 7.7%, Sorafenib 33.1%). Median survival in the total cohort was 15.0 months (mean 36.3±3.6 months). Patients with a score of 0 had a mean survival of 93.4±15.3 months (score ≤ 2: 42.9±6.0 months, score ≤ 4: 25.4±3.1 months score 4: 8.4±2.0 months). Differences between groups were significant. Validation in the Vienna cohort (n=1050, mean age 62.8 years, 82.5% male, 91.5% cirrhosis) yielded comparable results with statistical significant differences between the different score groups (score 0: mean survival 40.2±6.6 months, score ≤2: 33.9±2.4 months, score ≤4: 28.6±2.3 months, and score 4: 10.3±1.5 months). Separate analysis of platelet count in the Würzburg cohort showed a correlation to survival. Patients with a count >300x10³/mm³ had the shortest survival with 5.4 months (median) compared to 29.8 months (median) in the group with a count of 150-300x10³/mm³. Survival of patients with a count of <50 was 21.4 months, of patients with a count of 50-150 was 15.9 months.

Conclusion: A simple clinical score containing the parameters GOT, INR, platelet count and cirrhosis state could predict survival in patients with HCC. It seems to be driven substantially by the platelet count.

Impact of IGFBP2 on proliferation, migration and cell viability in hepatocellular carcinoma

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Background & Aim: 14 million patients worldwide are affected by hepatocellular carcinoma (HCC), the most common primary malignant neoplasia of the liver (85-90%), with the third highest tumor related mortality. The insulin like growth factor (IGF) system promotes growth and cell survival via IGF binding to the IGF receptor. IGF availability is regulated by insulin like growth factor binding proteins (IGFBPs) through competitive binding of IGF, thus limiting proliferative IGF effects. We previously identified IGFBP2 as a target gene of the p53 family - especially of p73 - in HCC. These tumor suppressors induce apoptosis or senescence as a reply to cellular stress signals. However, physiologic functions of p53-family induced IGFBP2 in HCC are so far unknown. Therefore, effects of IGFBP2 on HCC cell viability, proliferation and migration were studied and IGFBP2 induction by HCC-relevant therapeutics was evaluated.

Methods: Surface levels of IGF receptors and IGF secretion were analyzed in the human HCC cell line Hep3B. Cells were cultured with recombinant IGFBP2 (100 -1000 ng/ml). Subsequently, cell viability was determined by MTS assay, proliferation was determined by flow cytometry and cell migration was analyzed using a wound healing model. Moreover, activation of the IGF signaling pathway was measured by milliplex assay. Effects on RNA and protein levels of p73 and IGFBP2 by HCC-relevant therapeutics doxorubicin, bleomycin and regorafenib on IGFBP2 and p73 were analyzed by Western blot, qPCR and ELISA.

Results: Hep3B cells displayed an intact IGF system, indicated by constant IGF secretion over 96 hours and surface expression of insulin receptor and IGF receptor 1. Generally, cell viability increased time-dependently up to 115% after 96 hours using IGFBP2 concentrations between 100 and 500 ng/ml. IGFBP2 concentrations between 100 and 250 ng/ml resulted in a significant increase in proliferation of 16% and 18% and a decrease thereafter. Concordantly, enhanced cell migration was observed for IGFBP2 doses between 100 and 500 ng/ml after only 16 hours. Treatment with 100 and 1000 ng/ml recombinant IGFBP2 did not significantly alter the activation status of the IGF signaling pathway compared to the untreated control. Nevertheless, treatment of Hep3B cells with bleomycin, doxorubicin and regorafenib resulted in an induction of both TP73 and IGFBP2 on RNA and protein level.

Conclusion: IGFBP2, a growth-limiting factor within the IGF-system, was shown to be a p53 family target gene and was induced by HCC-relevant therapeutics together with the tumor suppressor p73. Conversely, IGFBP2 exerted proliferative effects in HCC cells when applied in a

recombinant manner. Since an induction of IGF signaling was not observed, the exact mechanisms of action need further elucidation. Taken together, we hypothesize that p53-family-mediated mechanisms must exist, which redirect IGFBP2-dependent signaling towards growth inhibition. Thus, detailed elucidation of signal transduction on the p73-IGFBP2-axis is indispensable to develop novel diagnostic and therapeutic options for HCC.

Serum levels of soluble programmed cell death-ligand 1 predicts prognosis in patients with hepatocellular carcinoma after curative treatments

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Background & Aims: Immunotherapy in hepatocellular carcinoma (HCC) is a recent and very promising approach, namely the inhibition of the PD/programmed death-ligand 1 (PD-L1) axis. After tumor ablation or surgical treatment, the 5 years recurrence rate is beyond 50%. Until now, no serum biomarker has proved to accurately discriminate patients who will develop recurrence from those who will not. In this prospective on-going clinical study we aim to investigate the prognostic value of a soluble form of PD-L1 in HCC patients.

Methods: During 2016 to 2019 a total number of 267 patients with HCC have been evaluated for possible inclusion in the study. In total, 123 patients with Child-Pugh class A, BCLC class 0 or A treated by either ablation (microwave or radiofrequency) or surgery were analyzed. Pre-treatment serum sPD-L1 levels were measured with an enzyme-linked immunosorbent assay (ELISA). Additionally, in 40 out of 123 patients sPD-L1 was also measured 4-6 weeks after ablation or surgery.

Results: Median sPD-L1 concentrations in patients with HCC was 95 (range 47.6-305.4) pg/mL. Using the cut-off value of 95 pg/mL, patients were stratified into low (< 95 pg/mL) and high sPD-L1 (\geq 95 pg/mL). 108 out of 123 had a minimum follow-up of at least 6 months. After a median follow-up of 18 months the recurrence rate was 10.63% in patients with low sPD-L1 compared to 68.85% in patients with high sPD-L1 ($p < 0.001$). Disease-free survival was 14.2 months compared to 6.3 months in low vs high sPD-L1 patients ($p=0.001$). In 23 out of 40 patients sPD-L1 increased 4-6 weeks after treatment, while in 17 out of 40 patients it remained stable or decreased.

Conclusion: We conclude that a high sPD-L1 level is a possible prognostic marker for a poor outcome in HCC patients after curative treatment. Patients with high sPD-L1 might benefit from combination therapies (e.g. tumor ablation and PD-1/PD-L1 inhibitors). Nevertheless, the predictive value of sPD-L1 levels for a successful anti-PD1/PD-L1 therapy should be investigated in the future.

Chemerin-156 reduces liver tumor growth *in vivo* but has no effect on liver cell proliferation and migration

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Background & Aim: Chemerin is an adipokine that is not only expressed in white adipocytes but also in hepatocytes at high levels. Chemerin functions in the regulation of glucose and lipid homeostasis, inflammation, adipogenesis and tumor growth. After secretion, prochemerin is processed into certain isoforms, which can activate the receptors chemokine-like receptor 1 and G-protein-coupled receptor 1 to varying extent. The most active isoforms of chemerin in mice are Chem-156 and Chem-155. The respective human isoforms are Chem-157 and Chem-156. In an orthotopic mouse model of hepatocellular carcinoma (HCC) Chem-156 reduces tumor growth (doi: 10.1038/onc.2016.516). Whether Chem-156 has a similar activity in carcinogen induced liver tumors and whether this or further isoforms impair proliferation and migration of hepatic tumor cells has not been analyzed in detail.

Methods: Two weeks old C3H/HeNRj mice were injected with diethylnitrosamine (DEN) to induce HCC. After six months, mice were infected with 1012 adenoassociated virus 8 (AAV8) particles to achieve a liver specific overexpression of Chem-156. Furthermore, to characterize the physiological function of chemerin in hepatocellular carcinoma Chem-157 and Chem-156 were overexpressed in the human hepatic cancer cell line HepG2 and the human stellate cell line LX-2. In addition, the murine Chem-156 and Chem-155 were overexpressed in the murine hepatoma cell line Hepa1-6. Migration of the cell lines was analyzed with scratch assays and proliferation levels were determined with measurement of cell numbers 24, 48 and 72 h after transfection.

Results: Serum chemerin levels and hepatic chemerin protein were higher in AAV8-Chem-156-injected mice compared to the AAV8-control-injected mice. Thereby, hepatic tumor burden was reduced by about 30 %. Interestingly, Chem-155 was the most abundant isoform in the liver while Chem-156 was only detected in two out of eight animals infected with Chem-156 producing AAV. This suggests that Chem-156 is processed to Chem-155 in the liver. However,

Chem-156 and Chem-155 or its human analogs have no effect on cell proliferation in Hepa1-6 cells, the murine hepatic stellate cell line LX-2 or HepG2 cells. Furthermore, migration of Hepa1-6 cells is not influenced by these overexpressed chemerin isoforms.

Conclusions: Chem-156 overexpression in the liver reduces hepatic tumor burden in the DEN-HCC model. Chem-156 seems to be converted to Chem-155 in the liver. However, both of these isoforms have no effect on cell proliferation or migration.

Cell death induction via energy depletion in hepatocellular carcinoma (HCC)

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Background & Aim: It is appreciated that there is an intense crosstalk between metabolism and signaling cascades regulating cell survival, proliferation and differentiation. Dimethyl fumarate is a diester of fumaric acid with methanol and an established pharmaceutical for psoriasis. We could show that treatment with DMF in different solid tumor cell lines (e.g. PC3, HCT116, MDM-MB231) resulted in an increased glycolysis rate and a decreased mitochondrial respiration. We assume that treatment with DMF results in energy depletion and, therefore, cell proliferation will be impaired and cell death will be induced.

Methods: Human liver tumor cell lines HepG2, Huh7 and Hep3B were treated with DMF (25 µM up to 100 µM) or 2-deoxyglucose (2DG) (1.1 mM up to 5.6 mM for HepG2 and Hep3B or 2.5 mM up to 12.5 mM for Huh7, depending on glucose concentration in the medium) and cultivated for up to 72 h. Induction of cell death was determined using a luminescence based viability assay. Characterization of DMF-induced cell death was performed by flow cytometry (FACS analysis) using 7AAD/Annexin V FITC staining.

Results: DMF application resulted in a time- and dose-dependent induction of cell death. Cell death in HepG2, Huh7 and Hep3B was triggered upon 48 h of treatment with DMF. The main effect on cell death was observed after 72 h and a concentration of 100 µM DMF. Cell death induction was determined by luminescence based viability assays and FACS analysis. In addition, cells were treated with inhibitors of glycolysis. HepG2, Huh7 and Hep3B cells were treated with 2 DG, an inhibitor of the Glucose-6-phosphat-isomerase. Subsequently, cell viability/cell death was analyzed. Cell death in HepG2, Huh7 and Hep3B was induced after 24 h of treatment. The greatest impact on cell death was observed with the highest concentration of 2DG.

Conclusion: Solid tumors – especially HCC – display a rather high mortality rate compared to other tumors. Here we show that DMF is capable to induce cell death in HCC

cell lines. DMF is already approved for treatment of psoriasis showing minor side effects compared to common anti-cancer drugs. Hence, targeting cellular metabolism by substances like DMF should be regarded as a promising approach to develop novel therapeutic tools to treat solid tumors such as HCC. In addition, 2DG is capable to induce cell death in liver tumor cell lines, which is caused by energy depletion. The combination of both drugs will be a challenging project for the future.

Induction of non-apoptotic cell death in hepatoma cell line HepG2 after treatment with new targeted therapies

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Background & Aim: Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide and is recognized as one of the most chemo-resistant tumor types. For patients with non-resectable HCC, the only systemic therapy option was treatment with sorafenib, a multikinase-inhibitor. This targeted therapy is only used in case of a well-preserved liver function (Child-Pugh A) and for patients with advanced tumors (BCLC-C) or earlier stage tumors unsuitable for loco-regional therapies. Since the new EASL guideline recommends novel therapeutic substances that have been admitted in July 2018, the systemic therapeutic repertoire for HCC is expanded. Tumor suppressor p53 is an essential regulator of cell death. Thus, it is not astonishing that – together with its family members p63 and p73 – it is the most mutated gene in human cancer. The aim of this study is to understand and elucidate the molecular pathways by which these novel drugs induce cell death in HCC.

Methods: The human HCC cell line HepG2 was incubated with serum concentrations of HCC-relevant therapeutics (lenvatinib 1.17 μ M, ramucirumab 3.48 μ M, bleomycin 2 μ M, regorafenib 5 μ M, sorafenib 4.5 μ M) for 24 - 72h. Cabozantinib and bleomycin were administered in 2x serum concentration (4 μ M and 2 μ M). DMSO treatment served as control. Drug-induced changes on mRNA level regarding the p53 family as well as pro-/anti-apoptotic members of the Bcl-2 family were evaluated by qPCR. In addition, levels of p53 family proteins were determined by Western blot. Cell viability was analyzed by MTS-Assay and cell death was determined via flow cytometry using DAPI/Annexin V staining.

Results: Viability of HepG2 cells was reduced by almost 50% after treatment with bleomycin, sorafenib, regorafenib and cabozantinib for 48h. However, flow cytometry analysis revealed that sorafenib and regorafenib treated cells did not display an apoptotic phenotype of cell death. Incubation with bleomycin resulted in increased protein levels of p53, whereas p63 and p73 remained unaffected. Incubation with targeted

therapies showed no increase in p53, p63, p73. Nevertheless, caspase cleavage as a characteristic feature of apoptosis was not detected and mRNA levels of proapoptotic Bcl-2 family members (Bax, Bak) were unchanged after treatment with sorafenib, regorafenib, cabozantinib.

Conclusion: Novel HCC therapies are able to initiate cell death in hepatoma cells. Even though p53 is induced by bleomycin but not by sorafenib, regorafenib and cabozantinib, cells die via a non-apoptosis pathway. Hence, these findings not only expand our knowledge concerning the mode of action of drugs administered in HCC, but also indicate that - apart from apoptosis - p53 is involved in other types of cell death of hepatoma cells.

Glucose / insulin metabolism disorders in patients with polycystic ovary syndrome and assisted reproductive technology

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Background & Aim: Polycystic Ovary Syndrome (PCOS) is considered a risk factor for infertility and the development of gestational diabetes mellitus (GDM). According to the international IVF recommendations, metformin is used in PCOS patients with infertility. The aim of this study was to determine the preconceptional rate of glucose metabolism disorders (GMD) and insulin resistance (IR) in PCOS patients as well as the GDM rate.

Material and Method: Retrospective data analysis of 153 PCOS patients with assisted re-productive technology (ART) treatment in a fertility center. Preconceptional Infertility Di-agnosis Level III including 75g-oGTT with testing of insulin resistance. In comparison, the common definition (D) of a preconceptional GMD / IR was supplemented and compared with the empirical definition (eD) (GMD: impaired Glc dynamics, GDM limit values / IR: empirical limit values exceeded). All patients were treated with metformin. At the time of a positive pregnancy test the patients were tested for GDM.

Results: 11.2% (D) / 63.9% (eD) of the PCOS patients showed a preconceptional GMD. 53.9% (D) / 86.2% (eD) showed a preconceptional IR. 61.4% conceived in the first IVF / ICSI cycle, 73.4% came to live birth. 50% developed GDM, 91.5% of them in early pregnancy. 6.4% developed overt diabetes mellitus during pregnancy. 87.2% of GDM patients were included in the empirical definition as a risk summary. The pregnancy rate was highest (76.9%) and the abortion rate was with almost 50% lower at 18.5% compared with 33.3% at a duration of use < 6 months in the case of a preconceptional metformin intake duration of \geq 6 months.

Conclusion: PCOS patients take benefit from preconceptional metformin intervention and ART treatment in metabolic controlled cycles. Preconceptionally detected

regulatory disorders in the glucose / insulin metabolism as well as the five-fold increased GDM rate in comparison to the literature make the preconceptional monitoring of the glucose metabolism a priority. The high pregnancy rate of the PCOS collective suggests a positive influence of a preconceptional testing of the glucose / insulin metabolism as well as an early screening for GDM in pregnancy.

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