Sibiu (Hermannstadt), Romania

The 5th Romanian-German Symposium of Gastroenterology in Sibiu, Romania

April 20–21, 2018

Symposium President:
Assoc. Prof. Dr. med. Paul Jürgen Porr

Program and Abstracts

Friday, April 20, 2018

Scientific Program, Aula Magna, University Lucian Blaga, Sibiu

8.50 – 9.00 Opening remarks (Assoc. Prof. Dr. med. Paul Jürgen Porr)

9.00 –10.40 Session I. Chair: Prof. Dr. med. Dr.h.c. Wolfram Zoller (Stuttgart)
Prof. Dr. med. Michael Sackmann (Bamberg)

9.00 – 9.20 *Alexander Hann (Ulm)*
Virtual reality in the training of young gastroenterologists.

9.20 – 9.40 *Michael Jung (Mainz)*
The problem of hygiene and disinfection in endoscopy. Lesions and consequences from the infections series of contaminated duodenoscopes.

9.40 – 10.00 *Wolfram Zoller (Stuttgart)*
Is there still a need for EUS-FNA in the light of contrast-harmonic endoscopic ultrasound?

10.00 -10.20 *Andrada Seicean (Cluj-Napoca)*
EUS and the new concept of endo-hepatology.

10.20 -10.40 *Michael Sackmann (Bamberg)*
Barrett's Esophagus: Prevention and screening.

10.40 – 11.00 Coffee Break

11.00-13.40 Session II. Chair: Prof. Dr. med. Wolfgang Stremmel (Heidelberg)
Prof. Dr. med. Tilo Andus (Stuttgart)

11.00-11.20 *Adrian Goldiș (Timișoara)*
Crohn's disease – regional differences and natural disease course: National and European trends.

11.20 -11.40 *Wolfgang Stremmel (Heidelberg)*
A new pathogenetic perspective of ulcerative colitis and its implication for therapy.

11.40-12.00 *Tilo Andus (Stuttgart)*
Inflammatory bowel disease – current medical treatment.

12.00-12.20 *Paul Jürgen Porr (Sibiu)*
Intestinal microbiota and its implications in digestive and extradigestive pathology.

12.20 -12.40 *Hartmut Köppen (Leipzig)*
Stool transplantation for Crohn's disease – a case report.

12.40-13.00 *Simona Bățagă (Târgu-Mureș)*
Colonic polyps, importance of polypectomy and of colo-rectal cancer screening.

13.00-13.20 *Anca Zimmermann (Mainz)*
Influence of malnutrition on DNA damage and the impact of early individualized nutritional intervention in patients with newly diagnosed gastrointestinal tumors.

13.20 -13.40 *Dan L. Dumitrașcu (Cluj-Napoca)*
Non-pharmacological therapy of the functional gastrointestinal disorders.

13.40 – 14.30 Lunch break and poster viewing Prof. Dr. med. Wolfram Zoller,
Prof. Dr. med. Monica Acalovschi

14.30-15.50 Session III. Chair: Prof. Dr. med. Helmut Karl Seitz (Heidelberg)
Prof. Dr. med. Markus Lerch (Greifswald)

14.30 – 14.50 *Ioan Sporea (Timișoara)*
Multiparametric ultrasound for liver evaluation. Multistep approach to a focal liver lesion (FLL).

14.50 -15.10 *Helmut Karl Seitz (Heidelberg)*
Alcoholic liver disease: Update 2018.

15.10 -15.30 *Sebastian Mueller (Heidelberg)*
Masked hemolysis as an important factor of iron overload in alcoholic liver disease.

15.30 – 15.50 *Monica Acalovschi (Cluj-Napoca)*
NAFDL, cholesterol gallstones and cholecystectomy.

15.50-16.10 Coffee Break

16.10-18.30 Session IV. Chair: Prof. Dr. med. Martina Müller-Schilling (Regensburg)
Prof. Dr. med. Peter R. Galle (Mainz)

16.10-16.30 *Robert Thimme (Freiburg)*
Novel concepts in the evaluation and treatment of liver cirrhosis.

16.30-16.50 *Roxana Şirli (Timişoara)*
The role of ultrasound-based elastography for the diagnosis of portal hypertension.

16.50-17.10 *Martina Müller-Schilling (Regensburg)*
Hepatocellular carcinoma: epidemiology, risk factors and current treatment strategies.

17.10 – 17.30 *Peter R. Galle (Mainz)*
Update of the EASL Clinical Practice Guideline on management of hepatocellular carcinoma.

17.30 – 17.50 *Zeno Spârchez (Cluj-Napoca)*
Role of contrast enhanced ultrasound in evaluating therapeutic response in hepatocellular carcinoma.

17.50-18.10 *Markus Lerch (Greifswald)*
The role of inflammation and inflammatory cells in pancreatitis.

18.10 – 18.30 *Joerg Köninger (Stuttgart)*
Standards in the surgical treatment of pancreatic cancer.

18.30 – 18.50 Closing remarks (Prof. Dr. med. Monica Acalovschi)

Session I

Virtual reality in the training of young gastroenterologists

Alexander Hann[1], Benjamin Walter[1], Niklas Mehlhase[1], Stefan Andreas Schmidt[2], Alexander Meining[1]

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Background: The standard setting in endoscopy at present is manual manipulation of the endoscope guided by the visual input of the screen mounted in front of the examiner. Virtual reality (VR) involving computer generated replica of the environment or adding useful information to the perceived environment, has the potential of replacing the traditional interaction between examiner and the 2D flat screen.

Methods: In this work we explored different application scenarios of VR in endoscopy to overcome common problems in daily work and improve the training experience of young gastroenterologists. The head mounted display HTC VIVE was used to visualize datasets generated during the gastroenterological work up. Training videos of different endoscopic procedures such as advanced polypectomy, closure of a perforation and treatment of gastrointestinal bleeding were recorded in a high definition quality. Additionally, a grab and pull navigation method through a CT colonography was designed and tested. The real-time endoscopic image was projected into VR with the implementation of an intuitive zoom due to the movement of the head forward during critical steps of the procedure. Finally we built an easy to use interactive presentation tool that can be used to create lectures about gastroenterological topics in VR. Using two cohorts we compared a lecture held in VR with a classic seminar regarding the same gastroenterological topic.

Results: We demonstrated the VR application with the examination of a virtual colon and endoscopic videos to 29 gastroenterologists in a hands-on training. The participants reported a low physical and mental demand during the training. Discomfort involving nausea and vertigo was rated as low. A lecture in VR about high resolution esophageal manometry resulted in a good overall impression. The exam results after the VR lecture were similar to those of the cohort that had the classic seminar.

Conclusion: Virtual reality has a great potential for improving daily work in endoscopy and help during the training of young gastroenterologists. Still interface problems such as acquiring 3D images using standard endoscopes need to be investigated in the future.

The problem of hygiene and disinfection in endoscopy. Lesions and consequences from the infectious series of contaminated endoscopes

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Infectious series due to contaminated duodenoscopes by multi drug resistant organisms (MDRO) have been reported in the last three years in the United States and Europe and have alarmed national authorities.

Common features of all series are similar: only lateral viewing endoscopes are concerned, and multi drug resistant bacteria – Carbapenem resistant, MRDO class 4 – were found. No breaches of the reprocessing protocol are observed in any of the institutions. But micro damages on the distal end of the endoscope were identified as one source of infection. In particular, the part around and behind the Albarran elevator of the duodenoscope was estimated for the entire part of bacterial residues and biofilms.

Flexible endoscopes are thermo-labile instruments and regarded as semi-critical, following the Spaulding classification. Due to their complex design, heat sterilization is not possible,

but meticulous reprocessing including cleaning, disinfection and drying before storage is therefore mandatory.

Inappropriate cleaning and disinfection may lead to moisture and biofilm formation in the small endoscope channels by forming protein plugs and less biocide susceptibility.

Efforts have been made to reduce the risk of contamination with different attempts: double reprocessing of high level disinfection led to reduction, but not the elimination of all germs. Ethylene oxide gaseous sterilization reduced the bacterial load considerably, but still not completely. But permanent microbiological testing identified critical endoscopes to sort out, so reducing the risk of bacterial transmission.

With regard to the alarming infections and problems of improper reprocessing, the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterologic Nurses and Associates (ESGENA) published guidelines to focus on the critical factors and potential weaknesses in flexible endoscope reprocessing (2017). The crucial points concern the design of endoscopes, in particular duodenoscopes, the possible contamination of fluids and accessories during reprocessing, and the personnel influence.

This statement emphasizes to intensify and optimize the whole process, validation and regular re-qualification of washer-disinfectors, and regular microbiological surveillance of endoscopes (every 3 months), of the whole equipment, as well as personal training and qualifications.

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Is there still a need for EUS-FNA in the light of contrast-harmonic endoscopic ultrasound?

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EUS-FNA has become routine practice in gastroenterology [1]. Established indications are, for instance, tumor staging, or lymphadenopathy of unknown origin. In case of uncertain pancreatic tumor, EUS-FNA has significant impact on patient´s management. Sensitivity and specificity for pancreatic tumor staging range between 85-89%, and 96-99%, respectively. In comparison to CT- or transabdominal ultrasound-guided biopsy, EUS-FNA harbours higher diagnostic accuracy, especially in smaller tumors. In case of mediastinal lymphadenopathy, EUS-FNA has higher sensitivity and specificity than EUS alone. Other relevant regions of interest for EUS-FNA are the adrenal glands, liver, ascites, or pleural effusion. Whereas complications after EUS-FNA of lymph nodes only rarely occur, FNA of pancreas, liver, ascites, or especially cystic lesions harbours an even small, but not irrelevant risk of complications, with relevant morbidity in up to 3.5% of the cases. False positive results have been reported in up to 5%, especially in case of a luminal tumor. Furthermore, there is still some concern about needle track tumor seeding.

Contrast-harmonic endoscopic ultrasound (CH-EUS) is a relatively new technique, adopting low-MI ultrasound contrast media to endoscopic ultrasound. Certain vascularization patterns are considered for differential diagnosis. Of special interest is the differentiation of the pancreatic tumors. Typically, adenocarcinomas are hypovascularized, whereas neuroendocrine tumors or focal tumor-like inflammations show a hyper- or isovascularization. In several studies [2, 4, 6, 7], differentiation of adenocarcinoma using CH-EUS was possible with a 92–96% sensitivity. Results for specificity ranged between 68 and 94%. Collaborating results for neurodendocrine tumors were 69-78%, and 90-98%, respectively. It is of special interest that CH-EUS correctly identified up to 5% of adenocarcinoma showing false-negative results with EUS-FNA. In case of IPMN, CH-EUS correctly identified malignant disease, significantly better than conventional EUS [5]. In case of uncertain subepithelial tumors, benign and malignant GISTs could be differentiated due to their perfusion pattern with 100% sensitivity. However, specificity was relatively low (63%) [8].

EUS-FNA, besides obtaining surgical specimens or clinical follow-up, was used as gold standard in most of the CH-EUS studies. Up to now, no direct comparison between EUS-FNA and CH-EUS has been published. A few studies investigated the effect of CH-EUS for targeting EUS-FNA. In CH-EUS targeted EUS-FNA, fewer needle passages were necessary to achieve a positive result [9]. However, CH-EUS-targeted FNA did not result in higher diagnostic accuracy [10]. Interobserver variability is a crucial issue in every diagnostic technique. In CH-EUS, results significantly differ between certain studies and different organs [3].

In conclusion, histology/cytology remains to be the gold standard. In certain indications, EUS-FNA and CH-EUS are of comparable sensitivity, while specificity is higher in EUS-FNA. In case of contraindications, or equivocal results of EUS-FNA, CH-EUS is a valuable technique. In daily clinical practice, EUS-FNA and CH-EUS are used complementary, and are not competing.

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EUS and the new concept of endo-hepatology

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Endoscopic ultrasound (EUS) has been developed for the visualization of the retroperitoneal space, but it is able to visualise properly the entire left lobe of the liver and the hepatic hilum.

When assessing a hepatic mass, the presence of components with two different echogenicity is suggestive of malignancy, while a hyperechoic well delineated lesion is considered as a hemangioma or a neuroendocrine tumor. Systematic assessment of the left hepatic lobe during EUS performed for staging or sampling of the eso-gastric or bilio-pancreatic tumors is required. EUS can detect occult metastasis not visualized on CT scan in 2 to 7% of cases.

EUS with fine needle aspiration is indicated for liver masses when a gastroscopy or EUS under sedation is scheduled and a liver biopsy has to be performed in the same patient. Another indication is when the percutaneous liver biopsy is contraindicated, due to important ascites, poor accessibility or visibility of the liver mass.

Portal vein pressure measurement in humans can be performed by EUS approach and treatment of gastric varices by directing the cyanoacrilat associated with/without coil injection, can be safely done. New experimental techniques such as the intrahepatic portosystemic shunt, the drainage of hepatic abscesses or the portal injection chemotherapy for treating liver metastases were described.

Barrett˙s esophagus: prevention and screening

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Barrett´s esophagus (BE) is prevalent in about 1-2 % of non-selected patients undergoing upper GI endoscopy. The incidence of Barrett´s carcinoma is steadily increasing in recent years, at least amongst Caucasians. The molecular pathway of the progression from reflux to BE to dysplasia and cancer has recently been clarified. However, strategies for prevention and screening of BE are yet to be fully substantiated.

Interestingly, body mass index is positively associated with the relative risk of BE, while body height is inversely correlated with BE and Barrett´s carcinoma. Consumers of alcohol, smokers, and patients with reflux symptoms are two times as likely to be diagnosed with BE.

According to a 2017 statement of the ESGE, screening of BE can be considered in the group of patients with gastro-esophageal reflux disease lasting for more than five years, aged 50 years or older, male, overweight patients, and those with relatives suffering from BE. ESGE recommends patients with a long-segment BE should undergo surveillance endoscopies in specialized centers; patients with BE of 3 to 9 cm length should have surveillance endoscopy every three years, those with BE of 1 to 2 cm every five years, and those with ultra-short BE most likely do not need surveillance endoscopies, respectively.

In a survey covering the Wiesbaden cohort of patients, other data from Germany, and recent international publications, the risk of Barrett´s carcinoma in patients with long-segment BE was reported to be more than twice as high as in those with short BE or ultra-short BE. To detect one Barrett´s carcinoma per year, n = 450 patients with long-segment BE had to be examined, whereas 3,440 endoscopic examinations were required to detect one

carcinoma in short-segment BE patients, and the astonishing number of 12,364 examinations was necessary in patients with ultra-short BE. According to another recent study, long-term use of NSAIDs did reduce the risk of Barrett´s carcinoma. In yet another study, the use of aspirin did not reduce this risk. Other research did not show clear benefit of the use of statins either.

In summary, essential recommendations for the prevention of BE include the reduction of overweight and the abstinence from alcohol and/or nicotine. Long-term use of NSAIDs but not of aspirin might reduce the risk of cancer development. Screening may be recommended for specific groups of patients.

Session II

Crohn's disease - regional differences and natural disease course: National and European trends

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Inflammatory Bowel Diseases (IBD), represented by ulcerative colitis (UC) and Crohn's disease (CD), are autoimmune conditions with a different geographic distribution, and also with a different outcome. In Romania, as shown in other countries, there is a North-South and East-West gradient of IBD incidence.

We used for this review two databases: the EpiCom, a population-based inception cohort of newly diagnosed IBD patients, which is a prospective study involving 31 European centers (14 from the West part and 8 from the East part of Europe), with 488 cases of CD out of all the 1515 IBD cases. The second register used was IBD Prospect, which is a Romanian prospective cohort, which started in 2006, and includes cases from 10 University Centers. The aim of this study was to determine if in our country CD respects the natural disease course that was described in Europe.

From the IBD Prospect, 2312 patients were analyzed, of whom 41.3% patients were diagnosed with CD, 56.3% with UC and 2.4 % with IBD unclassified (IBDU). From the EpiCom cohort, we analyzed 488 cases of CD (35% of total IBD) regarding disease behavior, medical treatment, surgery, hospitalization, cancer occurrence and death.

The complications of all IBD cases from Romania were registered. We found that 673 cases (33.4%) presented the following manifestations: arthritis 7.82% (181 cases), sacroileitis 3.37% (78 cases), erythema nodosum 1.29% (30 cases), pyoderma gangrenosum 0.60% (14 cases), uveitis 0.90 % (21 cases), renal lithiasis 1.64 % (38 cases), cholangitis 0.08% (2 cases) and other complications, totalling 265 cases (11.46 %). When we compared the distribution of cases in Romania, we noted that the region with the most subjects was East of the country (568/2312), while the North region had less cases (232/2312). Examining those data, we surmise that the most frequent complications occur in the Eastern part of Romania and among the CD cases.

From the EpiCom database, a total of 488 cases of CD were analyzed: 404 (83%) were diagnosed in Western Europe and 84 (17%) in Eastern Europe centers. Regarding disease behavior, a total of 141 subjects (29%) had complicated disease at diagnosis and after 5 years of follow-up there were 190 cases (39%). Progression in behavior was associated with colonic location and extra-intestinal manifestations. We observed geographic differences in the use of immunomodulators and biologics. Biologics were used in 144 cases (30%), more frequently in Western Europe (132 cases, 33%) than in Eastern Europe (12 cases, 14%). In total, 107 CD patients (22%) underwent a surgical intervention, in 62 (13%) surgery was performed during the first year after diagnosis. There were 89 surgical interventions from West Europe and 18 from Eastern Europe. From all those CD cases, 36% (175) were hospitalized because of IBD: 66 hospitalizations were related to surgery (38%), as compared to 109 (62%) for medical treatment. Only 8 subjects were diagnosed with cancer, all with extra-intestinal cancers. There were a total of 16 deaths, 2 related with CD (sepsis after surgery) and the remainder had non-CD causes.

Conclusions: There is a national trend of IBD cases, especially for CD that respects the pattern from Europe. The CD complications in our national database, although not so many as in the EpiCom cohort, involved a medical and surgical approach, statistically comparable with other centers from the Western part of Europe. The severity of new cases probably will need more and aggressive surgical and medical interventions in order to control the CD outcome.

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A new pathogenetic perspective of ulcerative colitis and its implication for therapy

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One component of the pathogenesis of ulcerative colitis is a disturbed mucosal barrier. The apical mucus layer prevents the commensal microbiota to invade. It is phosphatidylcholine (PC) bound to mucin2 which establishes the required hydrophobicity. In ulcerative colitis, the mucus PC content is intrinsically reduced by 70 %.

This is due to a diminished translocation of PC from systemic sources across the mucosal epithelium, mostly in ileum, to the mucus compartment. It was shown that this transport occurs across the lateral tight junction barrier driven by an electrochemical gradient generated by cystic fibrosis transmembrane conductance regulator (CFTR). This transport mechanism is disturbed in ulcerative colitis as a tight junctional disease.

The reduced mucus PC content lowers surface hydrophobicity and facilitates bacterial invasion with consequent mucosal inflammation. The colitis always starts in rectum and extends to upper colonic segments dependent on the degree of mucus PC depletion.

Accordingly, the working hypothesis was generated that topical supplementation of PC fills the open PC binding gaps on mucin2 and reestablishes a protective hydrophobic barrier. In a first proof-of-principle trial most of the active ulcerative colitis patients improved and more than half achieved clinical remission. Even in steroid refractory disease most of the patients could be withdrawn from steroids and at the same time improved in clinical and endoscopic activity.

The efficacy was proven in a multicenter phase IIB trial. The consequent phase III trial in mesalazine refractory patients was divided in an induction of remission trial and a maintenance of remission trial. Unfortunately, the induction of remission trial failed due to the simultaneous application of mesalazine, which, as a detergent neutralized the PC efficacy, prohibiting its integration into mucin2. However, the maintenance of remission trial showed in the experimental arm without application of mesalazine a beneficial effect.

In summary, a key pathogenetic feature of ulcerative colitis is a low mucus PC content. Topical supplementation of PC compensates this lack and prevents inflammation. Therefore, delayed release PC may add to the therapeutic armament for ulcerative colitis, in particular for maintenance of remission.

Inflammatory bowel disease – Current medical treatment

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Ulcerative colitis

Medical treatment led to a normalization of the life-expectancy of patients with inflammatory bowel disease. Furthermore, the risk of colorectal cancer of patients with pancolitis ulcerosa and colonic Crohn's disease decreased considerably. However, we still have no curative treatment, and about 50% of the Crohn's disease patients have chronic recurrent disease and have to be treated with corticosteroids, immunosuppressive drugs and biologics, which can lead to many side effects.

Standard treatment of mild-moderate ulcerative colitis consists of 5-aminosalicylic acid orally and/or rectally depending of the localization of the disease. More severe disease is treated with systemic corticosteroids such as prednisolone or sustained release corticosteroids. In steroid-dependent ulcerative colitis thiopurines (azathioprine or 6-thioguanine) or anti-TNF-antibodies (infliximab, adalimumab or golimumab), or anti-integrin-antibodies (vedolizumab) are required.

For the treatment of steroid-refractory ulcerative colitis, calcineurin-inhibitors (ciclosporine or tacrolimus) or anti-TNF-antibodies (infliximab, adalimumab or golimumab) are used. If these fail, and in severe cases, proctocolectomy should not be too long postponed.

For maintenance treatment 5-aminosalicylic acid orally and/or rectally can be used. If not possible, *E. coli Nissle* 1917 can be tried. Thiopurines (azathioprine or 6-thioguanine) or anti-TNF-antibodies (infliximab, adalimumab or golimumab) are used for 2nd-line maintenance treatment.

Crohn's disease

Mild – moderate Crohn's disease should be treated with oral budesonide orally. More severe cases with systemic corticosteroids. Steroid-dependent and -refractory patients need thiopurines (azathioprine or 6-thioguanine), methotrexate, anti-TNF-antibodies (infliximab, adalimumab), anti-integrin-antibodies (vedolizumab) or anti-IL12/IL-13 antibodies such as ustekinumab.

For maintenance treatment 5-aminosalicylic acid orally and/or rectally can be used in mild cases. Thiopurines (azathioprine or 6-thioguanine) or anti-TNF-antibodies (infliximab or adalimumab) are used for the 2nd-line maintenance treatment and in more severe cases.

Drug monitoring

Monitoring of serum levels of 6-thioguanine has been shown to be helpful to reduce the side effects and increase

efficacy of thioguanines for many years. Similar effects could be demonstrated for infliximab, adalimumab, vedolizumab and ustekinumab increasing clinical- and cost-efficacy.

Biosimilars

Recently, biosimilars for infliximab (inflextra, remsima, flixabi) were approved in the United States and in Europe. Up to now no significant difference could be found compared to the original formulation in spite of some differences in glycosylation and quarternary structure of the large proteins. However the question of the effect of multiple switching remains to be seen. In the near future we probably will have more drugs such as JAK-inhibitors like tofacitinib.

Intestinal microbiota and its implications in digestive and extra-digestive pathology

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Intestinal microbiota, influenced by genetic, nutritional and environmental factors, has multiple effects on the organism within a symbiotic relationship that makes our life possible. These effects have been uncovered at a very rapid pace in the last years, thus opening a new frontier in medicine.

At the level of the gastrointestinal tract, the disturbance of the microbiota balance, namely a dysbiosis, leads to acute or chronic enterocolitis, and even intestinal tuberculosis, Whipple's disease etc. An increasing phenomenon worldwide is pseudomembranous colitis determined by *Clostridium difficile*, mostly of an iatrogenic cause unfortunately. In the non-infectious pathology of the small bowel, such as in irritable bowel syndrome, inflammatory bowel disease (ulcerative colitis and Crohn's disease), and also in gastric and colon cancer, microbiota plays an important role. Through the entero-hepatic circulation it also has implications in hepatocellular carcinoma.

Numerous studies have been reported in the last years that document the complex roles of microbiota in metabolic diseases: the western diet determines a western type of dysbiosis, with a role in the onset of obesity, insulin resistance and type 2 diabetes mellitus. Atherosclerosis is also influenced by some dysbiosis, with well known cardiovascular consequences. Non-alcoholic fatty liver, and also the alcoholic liver diseases in all their forms (steatosis, steatohepatitis and cirrhosis) are also affected by dysbiotic states.

There is a clear evidence that atopy is due to a certain dysbiosis, leading to atopic dermatitis, allergic asthma and rhinitis.

The pathogenesis of many autoimmune diseases is also related to dysbiotic states that allow the penetration of the intestinal mucosa by antigens causing autoimmune conditions, either rheumatological (rheumatoid arthritis), hepatic (autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis), or neurological (multiple sclerosis, optic neuromyelitis).

Alzheimer's disease, with its pathogenesis heavily influenced by amyloid plaques, has also been proven to be related to a certain dysbiosis that determines the release of large amyloid amounts from polysaccharides.

In a number of psychiatric disorders, dysbiosis intervenes through the microbiome–bowel–brain axis, such as in depressive states, anxiety or anorexia. According to recent studies, even autism is influenced by certain states of dysbiosis.

All these observed facts have, besides a pathophysiological significance, a very practical and therapeutic importance, prompting for treating dysbiosis with pre- and probiotics, and thus indirectly improving the evolution of many of these related conditions.

Stool transplantation for Crohn's disease - a case report

Hartmut Köppen

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The composition of the human gut microbiome is influenced by genetic factors, our diet, drugs such as antibiotics, but also by the first colonization after birth. Impaired colonization, decreased biodiversity or additional risk factors such as caesarean delivery, antibiotic use or exclusive bottle feeding result in a shift in the microbiome. The ideal microbiome exhibits as much diversity as possible, is rich in both *Akkermansia muciniphila*, which stabilizes the intestinal barrier, and butyrate-formers, which nourish the mucosal cells, but low in gram negative proteobacteria.

Molecular genetic studies have shown a clear link between changes in the intestinal microbiome and Crohn's disease.

The intestinal microbiome in Crohn's disease is characterized by a low diversity, a decrease of *Faecalobacterium prausnitzii*, and of *Firmicutes* and *Roseburia* spec. On the other hand, an increase of proteobacteria such as enterobacteria and *E. coli* and clostridia is regularly observed in Crohn's disease.

If the therapy with probiotics and prebiotics does not succeed in an improved intestinal flora, a normal microbiome in its entirety can be reconstructed with a stool transplantation. Stool transplantation represents a novel therapeutic procedure. Worldwide, about 2000 patients have been treated with this procedure. There are currently no valid data regarding its long-term security.

In our practice, the chair transplantation is colonoscopic. The risks are similar to those from colonoscopy performed because of other indications. The main risk of stool transplantation is in the transmission of infectious agents, due to the foreign biological material used. In order to minimize this risk, a stool dispenser is chosen from the immediate family environment. Appropriate investigations are initiated for potentially transmissible diseases (viral hepatitis, HIV, syphilis and in particular intestinal pathogens). The donor stool is additionally examined for parasites.

We report on a 40-year-old patient who was a top athlete up to his illness, a severe Crohn's disease, about 5 years ago. When I saw the patient for the first time, he had been disabled for a year despite optimal therapy because of general frailty and

a cachectic state. After examining his intestinal microbiome and the microbiomes from his family environment, we decided to have a stool transplant. Already 3 days after receiving the transplant, he felt physically better. After a week, the bloody diarrhea had disappeared. About 4 weeks later, the patient had already gained 10 kg of body weight and achieved his normal body weight. He is now in excellent physical state and has started jogging again. In his current microbiome, all important butyrate-formers are again detectable, such as *Eubacterium* rectale and *E. hallii*, which are essential for the conversion of acetate and butyrate and which had previously been absent.

Noticeable is a marked increase in *Coprococcus* and *Akkermansia muciniphila*. Colonoscopically, the signs of inflammation have declined.

In summary, the stool transplant has led to a significant improvement in the microbiological findings. Clinically, the patient is doing much better now. The medication intake could be reduced. For the next few months, prebiotics (acacia fibers) are used to further increase the butyrate-formers.

Colonic polyps, importance of polypectomy and of colo-rectal cancer screening

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Colorectal cancer (CRC) is the second most common cancer in Europe and its incidence is steadily increasing. This trend is reversed in most of the European countries by screening. In the last twenty years, CRC screening programs in Europe have been implemented in most countries by using different methods: fecal occult blood testing, colonoscopy, transition from opportunistic to population based programs.

Colon cancer is one of the cancers that can be prevented by screening, as the precancerous condition is well known: polyps. Although colorectal polyps are precursors to colorectal cancer, it takes several years for these polyps to potentially transform into cancer. If colorectal polyps are detected early, they can be removed before this transformation occurs. It was believed that the time for a polyp to become malignant is about 10 years. However, in the last years a new group of polyps: sessile serrated polyps have been defined.

The sessile serrated polyps can potentially develop more aggressively into colorectal cancer as compared to other types of colorectal polyps and more rapidly, in about 3 years. The serrated pathway in tumorigenesis is associated with mutations in the BRAF or KRAS oncogenes, and CpG island methylation, which can lead to the silencing of mismatch repair genes and a more rapid progression to malignancy. Serrated polyps of the colorectum are the precursors of perhaps one-third of the colorectal cancers. They are located usually in the proximal colon and account for a disproportionate fraction of cancers identified after colonoscopy, i.e. "the interval cancers". ESGE recommends the routine use of high definition systems and pancolonic conventional or virtual (NBI) chromoendoscopy for better detection of serrated polyps.

In Romania, CRC is on the second place in men and on the third in women regarding incidence. Colon cancer incidence is still increasing in Romania. A CRC National screening has not been implemented yet; only opportunistic screening is being performed. The whole medical task force has to fight for the implementation of CRC screening and thus decreasing colon cancer incidence.

Influence of malnutrition on DNA damage and the impact of early, individualized nutritional intervention in patients with newly diagnosed gastrointestinal tumors

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Background: Malnutrition is often encountered in patients with gastrointestinal tumors (GIT). An individualized nutritional intervention before the start of treatment is associated with a better surgery outcome, shorter duration of hospitalization, fewer complications and less adverse effects of chemotherapy and radiation. DNA instability plays, next to the catabolic status, an important role. Possible associations between DNA damage and malnutrition and their reversibility by nutritional support have not yet been investigated. **Aim**: analysis of DNA damage at diagnosis of GIT and its modulation under nutritional intervention before the start of the treatment.

Patients and methods: Inclusion criteria: patients > 18 years with newly diagnosed GITs, who gave their written informed consent for participation in the study. The study was approved by the local Ethics Committee. We included 50 patients with a newly diagnosed GIT from the 1. Medical Clinic and Polyclinic and from the Clinic for General, Visceral and Transplantation Surgery of the University of Mainz. The patients were screened for malnutrition with the NRS questionnaire. Patients with an NRS ≥ 3 (n=44, 64.7 ± 10.7 years, 28M/16F, 10 with malignancies in the family history) received during the diagnostic workup and before the start of therapy (2-4 weeks) a nutritional counselling, followed by an individual fully balanced supplementation with ONS (oral nutritional supplementation) or – if necessary - parenteral nutrition. Clinical data were recorded in a pseudonymized manner. Blood samples were collected at start and before the beginning of treatment, for assessment of nutritional parameters and measurement of DNA damage by gammaH2AX immunofluorescence.

Results: During the short interval up to the start of therapy, patients experienced a stabilization of body weight, body mass index, total proteins and serum albumin, while prealbumin discretely increased (0.15±0.05 vs. 0.17±0,07 g/dl, n.s.), suggesting a stopping of the catabolic process. DNA damage in peripheral lymphocytes, measured at diagnosis, was increased (0.55±0.37 foci/cell in patients vs. 0.17±0.07 foci/cell in healthy controls; p=0.02). Under nutritional intervention, the number of DNA foci significantly decreased (0.24±0.21 foci/cell; p=0.04), suggesting a reduction of the DNA damage in a short time. The gammaH2AX-values were not different depending on nicotine or alcohol consumption, frequent flyer status or positive family history for malignancies.

Conclusions: This pilot study suggests for the first time that an early individualized nutritional intervention in the pretherapeutic phase of newly diagnosed GITs leads to a reduction of DNA damage, next to the stabilization of clinical and nutritional laboratory parameters. Further investigations in a larger patient group are required to define the role of DNA damage as a sensitive marker under early nutritional intervention in patients with newly diagnosed GITs.

Non-pharmacological therapy of IBS

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Bakground and Aim: Irritable bowel syndrome (IBS) is a challenging condition not only for patients but also for practitioners. A comprehensive approach includes not only pharmacological therapy but also life style recommendations and other therapies. The aim of this work is to review non-pharmacologcial interventions in IBS.

Methods: A literature search including own publications was undertaken in order to gather evidence concerning this topic. The most significant information was collected and compiled.

Results: A dietary pyramid for IBS has been recently published by our group, showing the most and the less indicated foods. FODMAP restrictions have offered contradictory results but the general advice is for FODMAP to be avoided by IBS patients. Psychotherapy is important and we show the main points of interventions in IBS and also the main therapeutic methods.

Conclusions: Non-pharmacological therapy is important in the management of IBS. It should never be neglected when therapeutic recommendations are offered to these patients.

Session III

Multiparametric ultrasound for liver evaluation. Multistep approach to a Focal Liver Lesion (FLL)

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Ultrasound became in the last years a clinical specialty, since, at least in a part of Europe (Germany, Italy or Romania), the procedure is performed mainly by clinicians, in many cases as a „point of care" method. The advantages of this approach are that the physician has the clinical information on the case, and there is no waiting time for the patient (the examination is performed in the consultation room).

On the other hand, ultrasound has become a very complex method, offering the opportunity to see the body structures in real time using ultrasound waves, and also to evaluate the vascularization (by Doppler or contrast enhanced ultrasound), and to assess the stiffness of different organs. Considering all the above, the term of „multiparametric ultrasound" seems reasonable when all these modalities for ultrasound evaluation are used.

In daily ultrasound evaluation of the abdomen, in many situations, focal liver lesions (FLL) are discovered (the so called „incidentalomas") and sometimes many tests have to be performed to elucidate their nature. Ultrasound, as in multiparametric US, is a good method for the assessment of such lesions and we propose a diagnostic algorithm. First, a standard ultrasound of the liver (and sometimes of other abdominal organs, such as the spleen) should be performed. The next step is to do an elastographic evaluation of the liver (and maybe of the spleen), because the presence of advanced fibrosis or cirrhosis of the liver probably means that the FLL discovered is a hepatocellular carcinoma. After this point, the evaluation of the FLL is different in a normal (non-fibrotic) liver or in cirrhotic patients.

The next investigation, with the same high tech ultrasound machine, is contrast- enhanced ultrasound (CEUS). Using one third or a half vial of SonoVue, in less than 5 minutes we can decide with an accuracy of 90% whether it is a benign or a malignant lesion, the accuracy of this method for the specific diagnosis of FLL type being 80-95% (1-3). Thus, in a high proportion of cases, the diagnosis is established „on site" and if a definite diagnosis cannot be obtained, another cross-sectional method (CE-CT or CE-MRI) should be used, and sometimes even liver biopsy.

This approach, using first multiparametric ultrasound as a „point of care" investigation, is the best approach, considering time and costs. Good quality ultrasound machines and trained specialists are indispensable for a rapid and beneficial evaluation of a patient.

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Alcoholic liver disease - Update 2018

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Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Europe. Histologically, several forms of ALD exist including hepatic steatosis, steatohepatitis (ASH), fibrosis, cirrhosis, and hepatocellular cancer (HCC).

One of the most severe forms of ALD is alcoholic hepatitis (AH), a clinical syndrome associated with liver failure and high mortality. Although most of the individuals consuming more than 60 grams of ethanol per day develop steatosis, a subset of patients develop AH and only 10 to 20% develop cirrhosis. Genetic, epigenetic and non-genetic factors might explain the considerable interindividual variation in the disease phenotype, severity and progression. The pathogenesis of ALD includes increased hepatic fat accumulation, oxidative stress, acetaldehyde mediated toxicity, and cytokine/chemokine mediated inflammation triggered primarily through gut-derived endotoxins. Diagnosis of ALD includes the patient's history, clinical signs of alcohol dependency and/or of advanced liver disease, and a typical liver laboratory profile including serum gamma-glutamyltransferase (GGT) activity as well as the ratio of serum AST to ALT activities. The degree of fat and fibrosis can be determined best through controlled attenuation parameter (CAP) and through transient elastography (Fibroscan). To date, limited specific medical intervention exists. Alcohol abstinence achieved by psychosomatic intervention occasionally flanked by pharmacological therapy is the best treatment for all stages of ALD. Therapy of alcoholic cirrhosis includes the treatment of its complications similar as in cirrhosis of other etiologies and liver transplantation (LT). In severe AH determined through various prognostic scores, hyperalimentation combined with prednisolone and N-acetylcysteine is the therapy of choice. Liver transplantation in AH is presently under evaluation.

Masked hemolysis as an important factor of iron overload in alcoholic liver disease

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Background and Aims: Patients with alcoholic liver disease (ALD) develop in ca. 50% prognostically unfavourable hepatic iron overload (HIO) and anemia. However, the underlying molecular mechanisms and the role of the systemic iron masterswitch hepcidin are poorly understood. Herein, we identify hemolysis as a novel factor in disrupting hepcidin regulation and eventually causing HIO.

Method: Iron-related parameters, hepcidin (mRNA and serum levels), molecular and laboratory markers were studied in a large cohort of Caucasian heavy drinkers (n=831, age range 22-87 years, mean alcohol consumption 192 g/day). Severe and mild hemolysis was further studied *in vivo* in age-matched C57BL/6 mice using two different phenylhydrazine (PHZ) treatment regimens. Histology, iron stain, mRNA and protein expression were studied both in the liver and spleen. An erythrophagocytosis model (oxidized red blood cells co-cultivated with differentiated human THP-1 macrophages) was finally used to recapitulate *in vivo* findings and to analyse the underlying mechanisms *in vitro.*

Results: Indirect evidence for hemolysis (anemia, high ferritin, high LDH, high MCV) as a cause for HIO was found in 16.4% of a large population of heavy drinkers. Notably, further indicators of hemolysis (haptoglobin, B12, folic acid) were not significantly changed most likely due to impaired liver synthesis. Despite higher ferritin levels as compared to controls, hepcidin was not adequately upregulated in the hemolysis group suggesting a suppressive effect of hemolysis. We next recapitulated suppression of hepcidin in a murine model of severe PHZ-induced hemolysis. PHZ induced severe anemia, elevated transaminases, transferrin saturation and LDH within 24 hours. In the same time period, hemoxygenase 1 was highly induced while hepcidin was significantly lowered by 50%. Histology confirmed an increased number of phagocytosed erythrocytes in the spleen and iron-loaded Kupffer cells in the liver. In contrast, the mild hemolysis model strongly upregulated hepcidin mRNA. We finally studied *in vitro* the process of erythrophagocytosis in human primary macrophages exposed to oxidized red blood cells. In confirmation of the *in vivo* findings, hepcidin showed also a concentration-dependent biphasic response. At physiological low levels of oxidized erythrocytes found as a normal age-mediated turnover, hepcidin was induced while it was strongly suppressed at higher pathological levels of oxidized erythrocytes.

Conclusion: Our data suggest that suppression of hepcidin by masked hemolysis seems to be an important mechanism leading to hepatic iron overload in patients with ALD.

NAFLD, cholesterol gallstones and cholecystectomy

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Non-alcoholic fatty liver disease (NAFLD) is an increasingly common chronic liver disease around the world with a diverse histopathological spectrum ranging from simple steatosis without significant inflammation to steatohepatitis with varying stages of fibrosis and, ultimately, cirrhosis and hepatocellular carcinoma. It is well known that NAFLD occurs more frequently in obese and diabetics, being currently considered as the hepatic manifestation of the metabolic syndrome (MetS). Although the molecular mechanisms involved in the pathogenesis of NAFLD and progression to NASH remain incompletely defined, most investigations indicate that insulin resistance plays an important role in NAFLD setup.

Liver insulin resistance is a key phenomenon for cholesterol gallstone formation. Risk factors for cholesterol gallstone disease (GSD) are consequently most MetS-associated disease conditions, such as obesity, type 2 diabetes mellitus and atherosclerosis. Frequency of both GSD and of NAFLD increases with age. Consistent with the shared risk factors, association between NAFLD and GSD in a same patient is common in clinical practice. Epidemiologic studies have confirmed the higher prevalence of cholesterol GSD in patients with NAFLD,

and also, conversely, the higher prevalence of NAFLD in patients with GSD. Presence of GSD was even shown to influence the severity of NAFLD.

Although the epidemiologic studies showing increased association of the two diseases suggest that they are linked pathogenically, their relationship is very complex and incompletely elucidated. The role of bile acids as key signalling is of major importance. Dysregulation of the farnesoid-X-receptor (FXR) may promote both GSD and NAFLD, and is now being studied as a potential therapeutic target for both diseases [2].

Moreover, recent evidence suggests that cholecystectomy itself might represent a risk factor for NAFLD. Although the underlying mechanisms of this effect are unknown, it has been suggested that gallbladder ablation may have metabolic and hormonal consequences [3]. Cholecystectomy might contribute to the development of NAFLD by altering the downstream signaling pathways of the bile acids related to hepatic lipid and glucose metabolism.

The recent EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones [4] underlined that the pathogenesis of gallstones in patients with fatty liver disease represents one of the most important areas of research in cholesterol GSD for the future.

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Session IV

Novel concepts in the evaluation and treatment of liver cirrhosis

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Liver cirrhosis is an irreversible stage of liver fibrosis and a leading cause of death world-wide. Clinical complications of liver cirrhosis include portal hypertension, decompensation including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, the hepatorenal syndrome and hepatocellular carcinoma.

Major causes of liver cirrhosis include chronic viral hepatitis, alcoholism and increasingly non-alcoholic steatohepatitis. Diagnosis of cirrhosis is primarily based on the combination of clinical manifestations, laboratory findings and abdominal imaging suggesting or confirming liver cirrhosis. Clearly, the first step after diagnosis of liver cirrhosis is the identification of the cause of cirrhosis. In most cases of an underlying liver disease, well-established therapies are available. Importantly, treatment of these underlying liver diseases can slow or even reverse progression of liver disease and in the case of hepatitis B virus (HBV) can even lead to reversion of liver cirrhosis. For hepatitis C virus (HCV), this information is currently not available. However, it can be expected that similar findings will also be made for HCV as direct acting antivirals have revolutionized treatment of HCV in recent years leading to sustained virological response rates of more than 90%. At diagnosis of liver cirrhosis, patients should also be screened for possible complications, especially, the presence of esophageal varices by endoscopy. In the case of ascites, puncture should be performed to rule out other causes of ascites as well as a spontaneous bacterial peritonitis.

After diagnosis of liver cirrhosis and initiation of therapy of underlying liver disease, patient should be advised to discontinue harmful medication and to avoid alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), herbal supplements or raw fish. All patients should be considered for liver transplantation if appropriate. Routine follow-up of patients with liver cirrhosis should occur every six months. Typical medications for patients with liver cirrhosis include beta blockers for primary or secondary treatment of esophageal varices, loop diuretics and aldosterone antagonist for treatment of ascites and lactulose and possibly Rifaximin for the treatment of hepatic encephalopathy. Next to the development of novel strong therapies for underlying liver diseases and liver cirrhosis, there has also been progress in the treatment of complications of liver cirrhosis. For example, novel procedures for the therapy of refractory ascites have been developed next to the transjugular intrahepatic portosystemic shunt, specifically, the alpha-pump. Also, for treatment of hepatocellular carcinoma, Regorafenib has recently been approved as a second-line therapy for patients showing progression under Sorafenib therapy. It can also be expected that checkpoint inhibitor therapy will have impact on treatment of HCC based on recent phase II trials. Check point inhibitor therapy might be combined with local ablative therapies or tyrosine kinase inhibitors, such as Sorafenib. In the presentation, these novel concepts in the treatment of the underlined diseases as well as the complications of liver cirrhosis will be discussed in more detail.

The role of ultrasound-based elastography for the diagnosis of portal hypertension

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Progressive fibrosis is encountered in almost all chronic liver diseases. Liver biopsy is still considered the reference method for staging the severity of fibrosis, but due to its

drawbacks (inter and intra-observer variability, sampling errors, unequal distribution of fibrosis in the liver, and risk of complications and even death), non-invasive methods were developed to assess fibrosis (biological and elastographic). Elastographic methods can be ultrasound-based or magnetic resonance imaging-based. According to the international and national guidelines, ultrasound-based elastographic methods are divided into strain/displacement elastography and shear waves elastography techniques [1-3]. The last category includes Transient Elastography (TE), point shear wave elastography using Acoustic Radiation Force Impulse (ARFI) technology (Virtual Touch Quantification – VTQ and ElastPQ), and real-time shear wave elastography (including 2D-SWE and 3D-SWE) [1-3].

It is a known fact that patients with advanced cirrhosis have shorter survival rates due to severe complications such as portal hypertension (development of esophageal varices, EV), hepatocellular carcinoma (HCC), and hepato-renal syndrome. Thus, it would be advantageous to identify the patients who are at risk for these complications, ideally by non-invasive methods. Since all ultrasound-based elastographic methods are valuable for the early diagnosis of cirrhosis, it seems reasonable to try to use them for the early prediction of these complications. The most precise evaluation of portal hypertension (PH) is the invasive measurement of hepatic venous pressure gradient (HVPG). A HVPG > 10 mmHg defines clinically significant PH (CSPH), with high risk of variceal bleeding [4]. In clinical practice, the size of esophageal varices is used to assess the bleeding risk.

Transient elastography is a promising method for predicting portal hypertension in cirrhotic patients, but it cannot replace upper digestive endoscopy or the invasive measurement of HVPG [5, 6]. However, recent guidelines recognize the value of TE to stratify patients at high risk to develop CSPH. Thus, it is considered that patients with a liver stiffness < 20 kPa and with a platelet count > 150,000/mm^3 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy [4].

The diagnostic accuracy of VTQ-ARFI in the liver to predict portal hypertension in cirrhotic patients is debatable, with controversial results in the published studies. The accuracy of VTQ-ARFI elastography may be significantly increased if spleen stiffness is assessed, either alone or in combination with liver stiffness and other parameters. Two-dimensional shear-wave elastography, the ElastPQ technique and strain elastography all need to be further evaluated as predictors of portal hypertension.

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Hepatocellular carcinoma: epidemiology, risk factors and current treatment strategies

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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). Hepatocellular carcinoma is the complication of chronic liver diseases and usually develops within liver cirrhosis related to different etiologies. In Asia and Africa hepatitis B virus infection (HBV) with or without aflatoxin B1 exposure, is the most frequent etiology, whereas hepatitis C virus infection (HCV), chronic alcohol abuse and metabolic syndrome are most frequently related to HCC in Western countries.

Because more than 90% of liver cancers arise in patients with underlying cirrhosis, the treatment approach for HCC depends on the stage and extent of the disease, the severity of the underlying liver disease and the overall performance status of the patient. Treatment consists of four strategies: 1. surgery (resection and liver transplantation); 2. locoregional procedures (ablation and transarterial embolization); 3. systemic therapies, and 4. best supportive care (BSC).

For patients with early-stage tumors, surgical treatment or ablation can be curative. Transarterial chemoembolization (TACE) can be offered to patients with intermediate stage HCC no longer amenable to cure. Systemic therapy is reserved for patients with advanced or unresectable disease. For the past decade (since 2007) the tyrosine kinase inhibitor Sorafenib was the only available standard of care for systemic treatment of advanced HCC. In a phase 3 trial, lenvatinib was non-inferior to sorafenib in overall survival in patients with untreated advanced HCC. The safety and tolerability profiles of lenvatinib were consistent with those previously observed. In April 2017, the US Food and Drug Administration approved regorafenib for the patients with HCC who had 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. Despite these recent phase three trials, which introduced new antiangiogenic therapies in both, first

line i.e. lenvatinib and second line treatment i.e. regorafenib and cabozantinib, HCC is in need for additional molecular treatments in first- and second-line therapy and also in the adjuvant setting. New data from international multi-centric genome sequencing projects are suggesting further promising therapeutic targets. For individualized patient care, genomic alterations identified in targetable genes will be useful to identify patients with HCC who could benefit from specific targeted therapies in clinical trials.

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 indications for ipilimumab (anti-CTLA-4 antibody) and nivolumab (anti-PD-1 antibody), which were first approved for the treatment of malignant melanoma, are expanding.

Clinical trials are currently ongoing to evaluate the utility of antibodies against programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) as monotherapy or combination therapy in patients with 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. This is the first approval of a cancer treatment based on defined genetic alterations rather than the organ where the tumor originated.

The randomized, double-blind, placebo-controlled phase 3 KEYNOTE-240 study compares efficacy and safety of the anti–programmed death 1 antibody pembrolizumab + BSC versus placebo + BSC in patients with previously treated advanced HCC.

In view of the new options in the treatment of HCC combining targeted agents and immune checkpoint inhibitors, adequate selection of a therapeutic strategy ideally based on specific biomarkers will become an important future challenge.

Update of the EASL Clinical Practice Guideline on management of hepatocellular carcinoma

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In 2012, the previous guideline for the management of hepatocellular carcinoma (HCC) was published as a result of a joint effort by the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC). Since then, several clinical and scientific advances have been achieved. Thus, an updated version of the document is needed. For this purpose, EASL established a guideline development group composed of international experts in the field of HCC, comprising the areas of hepatology (Peter R. Galle, Alejandro Forner, Josep Llovet, Fabio Psicaglia), surgery (Vincenzo Mazzaferro), radiology (Valerie Vilgrain), oncology (Jean-Luc Raoul) and pathology (Peter Schirmacher). The process was moderated by a methodologist (Markus Follmann).

In a first step the panel identified, prioritised and selected relevant topics and agreed on key questions to be answered. These questions were clustered and distributed according to the defined working groups, which are reflected in the different chapters.

According to the key questions, a literature search was performed. The studies identified and included were assessed and assigned to categories related to study design and strength of evidence according to endpoints. Based on this evidence, the drafts for recommendation and chapters were created.

Consent was provided for all recommendations during the consensus conference. Formal consensus methodology (nominal group technique) was used to agree upon the recommendations. All expert panel members were entitled to vote on the recommendations. The consensus conference was performed as a personal meeting over two days (in June and September 2017). When evaluating the evidence, the balance of benefits and harms, and the quality of the evidence were taken into consideration. Expert opinion and experience was included, particularly, if the body of evidence was insufficient and if further aspects such as time and costs, additional side effects, quality of life, resource use, etc. had to be considered.

The presentation will give an overview and focus on changes compared to the previous version.

Role of contrast enhanced ultrasound in evaluating therapeutic response in hepatocellular carcinoma

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Percutaneous ablative methods guided by imaging techniques are considered nowadays a curative treatment for early hepatocellular carcinoma (HCC) in patients who are not candidates for liver transplantation and surgical resection. The final goal of all ablative treatments is to achieve complete destruction of the neoplastic tissue by disruption of tumor vascularity. The best way to demonstrate the efficacy of any ablative methods noninvasively is to demonstrate that the blood supply has been disrupted both inside and at the periphery of the tumor by means of imaging methods. Contrast-enhanced ultrasound, using second generation contrast agents (CEUS) is almost as sensitive as contrast-enhanced computer tomography (CECT) (considered to be the gold standard) in depicting the residual tumor after ablation. Moreover, CEUS can be used before ablation to plan the treatment, during the procedure to guide the needle insertion or immediately after, to determine whether the tumor has been ablated or needs additional treatment that can be performed in the same session.

In the intermediate stage, transarterial chemoembolization (TACE) is considered an effective treatment for HCC. The most important independent prognostic factor of both disease free

survival and overall survival (OS) is the presence of complete necrosis. Therefore, treatment outcomes are dictated by the proper use of radiological imaging. Current guidelines recommend CECT as the standard imaging technique for evaluating the therapeutic response in patients with HCC after TACE. One of the most important disadvantages of CECT is the overestimation of tumor response. As an attempt to overcome this limitation, CEUS has gained particular attention as an imaging modality in HCC patients after TACE. Of all available imaging modalities, CEUS performs better in the early and very early assessment of TACE especially after lipiodol TACE. As all other imaging techniques, CEUS has disadvantages especially in hypovascular or multiple tumors.

For patients with advanced stage HCC, sorafenib demonstrated a significant improvement in OS and in the median time to radiologic progression. The response rate (RR) as assessed by the Response Evaluation Criteria in Solid Tumor (RECIST) which use the change in tumor size as a response parameter is no longer used to evaluate response as it underestimates the response rate. The estimation of the reduction in the viable tumor area using contrast-enhanced radiological imaging is considered nowadays the optimal method to assess treatment response. Based on these recommendations, in 2010 an adaptation of RECIST, termed modified RECIST (mRECIST) was designed specifically for HCC. According to mRECIST, the target lesion, is no longer the whole lesion but only the contrast-enhanced portion of the hepatic lesion at the arterial phase of a dynamic imaging technique such as a CT scan or magnetic resonance image. Using CEUS, it is now possible to quantitatively assess tumor perfusion by analyzing the linear raw data received by the US scanner or to analyze the quasi-logarithmic compressed data displayed on the video screen . Using specific perfusion parameters (peak intensity, latency time, time to peak intensity, maximal intensity value a.o.) it is possible to evaluate early responses (as early as 3 days after treatment start) to targeted agents in various solid tumors including HCC. However, this type of imaging named parametric CEUS requires optimal, standardized and fully reproducible imaging conditions using the same scanning plan. Using CEUS and mRECIST criteria, it is possible to assess the extent of necrosis induced by sorafenib in HCC and to calculate the response type. It has been demonstrated that the responders (those with complete and partial response) according to mRECIST had significantly longer mean OS compared to the non-responders. The recent findings strongly support the use of CEUS and mRECIST in evaluating the treatment with sorafenib in patients with HCC in clinical practice. The CEUS mRECIST evaluation of viable tissue changes after sorafenib (or other antiangiogenic drugs) although simply and practically it has some limitations: 1) difficulty to assess the response in the same plane and 2) the presence of discontinuous or multinodular tumoral enhancement both before and after treatment which may misinterpret the volumetric extent of remained enhanced areas using a simple 2D measurement.

The current limitations of CEUS in evaluating response after loco-regional or systemic treatment will be overcome by the new CEUS techniques that have been already tested in clinical practice, such as dynamic CEUS with quantification, three-dimensional CEUS or fusion techniques.

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The role of inflammation and inflammatory cells in pancreatitis

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For more than a century it has been assumed that pancreatitis is essentially a disease of autodigestion of the pancreas by its own proteases – most prominently trypsin. This view was greatly supported by the discovery that mutations in trypsin and other proteases are the most common genetic susceptibility factors for pancreatitis [1]. On the cellular level either the exposure to toxic levels of stimulants [2] or the transient obstruction of the pancreatic duct by a migrating gallstone [3] was shown to trigger the intracellular activation of trypsin mediated via the lysosomal hydrolase cathepsin B [4]. Although evidence, specifically from genetic studies, keeps accumulation that clearly suggests a connection between premature protease activation and the pathogenesis of pancreatitis [5], studies involving pancreatic exocrine (acinar) cells have recently suggested a more differentiated view on the intracellular events that precede tissue injury. In these the role of trypsin activity now appears much less prominent and either involves the degradation of harmful proteases [6] or restricts

the role of trypsin to that of an initial trigger, whose proteolytic activity has no bearing on the subsequent disease severity [7]. Instead, factors unrelated to intrapancreatic protease activity such as vascular mediators [8], the balance between extracellular matrix synthesis and matrix degradation [9] and the role of complement component 5 [10] have moved into the focus of research investigating either the progression from acute to chronic pancreatitis or the systemic inflammatory process. It is becoming increasingly clear that both processes are driven largely by tissue infiltrating inflammatory cells [11], rather than by proteases released from injured acinar cells [6]. First direct evidence for this connection came from studies in which tumor necrosis factor alpha, secreted from inflammatory cells was found to trigger trypsinogen activation in acinar cells in a cathepsin-B-dependent manner [12]. Rather than supramaximal concentrations of secretagogues which have long been known to induce protease activation, inflammatory cells are now regarded as an agent that triggers this process and induces acinar cell injury directly. In further studies it was found that resident and infiltrating macrophages endocytose acinar cell components including zymogen granules, that this is followed by a conversion of trypsinogen to active trypsin within the macrophage, and that intra-macrophage trypsin activity acts as a powerful damage-associated molecular pattern (DAMP), which leads to macrophage activation [13]. Previously, the role of inflammatory cells was undisputed in the context of autoimmune pancreatitis [14, 15]. It is now becoming increasingly clear that the formation of - and the recovery from - pancreatic tissue necrosis, as well as the progression to chronic fibrosis depend on the interplay between different classes of inflammatory cells including neutrophils, macrophages and T-cells [16].

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Standards in the surgical treatment of pancreatic cancer

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Surgical resection for pancreatic cancer remains a major challenge for every visceral surgeon. Approximately 15-20% of patients suffering from pancreatic carcinoma will be found to be eligible for resection at the time of diagnosis. In these cases, surgical removal of the tumor provides the best chance for cure and shows a better prognosis when compared to medical therapy. Today, 5-year survival rates of patients who underwent surgical resection for pancreatic cancer are reported to range between 20 and 25%.

In high volume centers, pancreatic resections can be performed with death rates below 5%. Still, the morbidity following pancreatic resection remains relevant. Around 30% of patients will suffer from some kind of perioperative complications including pancreatic fistula, wound infection, or delayed gastric emptying.

Today, venous resections including segmental resections of the portal vein should be standard procedures and are a measurement for quality of surgical resections for pancreatic cancer. Morbidity and mortality for venous resections are comparable to standard pancreatectomy. Moreover, it is reported that histologically confirmed portal vein infiltration does not segregate prognostically from other tumors. In contrast, arterial en bloc resection for pancreatic carcinoma is only meaningful in selected cases. Studies have shown

that superior mesenteric artery resection does not result in a survival benefit.

Patients with pancreatic cancer benefit from multivisceral resections when indicated. Moreover, resection of pancreatic cancer metastasis or resection of local recurrence can be meaningful in selected cases. Modern chemotherapy protocols together with improvements in surgical expertise have resulted in extended operations, pushing the borders of resectability. Multivisceral resections with or without resection of major mesenteric vessels are now performed in numerous patients, resulting in better outcome. Interdisciplinary tumor board decisions in specialized pancreatic centers are necessary to find the best treatment modality for each patient.

LIST OF POSTERS

1. Smoking is a risk factor for the development of esophago-respiratory fistula in esophageal cancer: a case control study
Gregor Paul, Wolfram Bohle, Wolfram Zoller
Department of General Internal Medicine and Gastroenterology, Katharinenhospital, Stuttgart, Germany

2. Statin use and premalignant gastric lesions in patients with chronic cardiovascular diseases
Monica Pantea[1], Anca Negovan[1], Septimiu Moldovan[2], Simona Mocan[3], Kinga Sárkány[1], Simona Bățagă[4]
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3. Differences of spleen and liver stiffness between alcoholic liver disease and HCV hepatitis: Cross sectional analysis and response to treatment
Omar Elshaarawy, Johannes Mueller, Shuai Lan, Helmut K. Seitz, Sebastian Mueller
Department of Medicine and Center for Alcohol Research, Salem Medical Center, University of Heidelberg, Heidelberg, Germany

4. Low lysophosphatidylcholine levels may predict severe alcoholic hepatitis
Adelina Horhat[1], Petra Fischer[1,2], Crina Grigoraș[2], Corina Hebrișteanu[3], Bogdan Procopeț[1,2], Carmen Socaciu[3], Horia Stefănescu[1]
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5. Liver stiffness values using 2d-SWE-Toshiba in healthy subjects
Alexandru Popa, Roxana Sirli, Alina Popescu, Alin Lazar, Cristina Apetrei, Camelia Foncea, Ruxandra Mare, Raluca Lupusoru, Ioan Sporea
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6. The value of ElastPQ to rule in and rule out HCV liver cirrhosis
Felix Bende, Ioan Sporea, Ruxandra Mare, Alina Popescu, Roxana Sirli, Mirela Danila, Renata Fofiu, Bogdan Miutescu
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7. Diagnostic accuracy of three non-invasive methods to evaluate fibrosis in patients with HCV compensated liver cirrhosis
Alin Lazăr, Raluca Lupușoru, Roxana Șirli, Alina Popescu, Felix Bende, Ruxandra Mare, Ana-Maria Stepan, Anda Pascaru, Virgil Ardelean, Isabel Dan, Alexandra Deleanu, Alexandru Popa, Cristina Apetrei, Ioan Sporea
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8. The value of ElastPQ and thrombocytes count for predicting presence of high risk varices
Renata Fofiu, Ioan Sporea, Felix Bende, Ruxandra Mare, Bogdan Miutescu, Alina Popescu, Roxana Sirli
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9. Bacterial infections and antibiotic spectrum in cirrhotic patients
Ruxandra Mare, Ioan Sporea, Andra Barbulescu, Renata Fofiu, Victor Baldea, Alina Popescu, Roxana Sirli
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10. Contrast enhanced versus conventional ultrasound guided liver biopsy in the diagnosis of hepatocellular carcinoma: A prospective study
Tudor Mocan[1], Pompilia Radu[1], Teodor Zaharia[1], Cristina Cebotaru[2], Gabriel Kacso[2], Nadim Al Hajjar[3], Zeno Sparchez[1,4]
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11. Diagnostic accuracy of contrast-enhanced ultrasound algorithm (ACR CEUS LI-RADSv 2016) for the diagnosis of hepatocellular carcinoma in patients with chronic liver disease
Ana-Maria Stepan, Mirela Danila, Roxana Sirli, Alina Popescu, Tudor Moga, Cristian Ivascu, Corina Pienar, Ioan Sporea
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12. Multiparametric Ultrasound algorithm for the reevaluation of inconclusive focal liver lesions evaluated by contrast enhanced ultrasound
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13. Sphingolipids – new biomarkers for detection of early and intermediate hepatocellular carcinoma
Iuliana Nenu[1], Andreea-Bianca Ardelean[1], Cristina-Nelida Bora[1], Sorana Paşcalău[1] , Horia Stefănescu[1], Bogdan Procopeț[1,2], Carmen Socaciu[3], Andrada Seicean[1,2], Zeno Sparchez[1,2], Marcel Tantau[1,2], Mircea Grigorescu[1,2]
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14. Delirium – of outstanding relevance for the interprofessional team on an intensive care unit with focus on hepatology
Lidia Cosma, Alexander Denk, Vlad Pavel, Constantin Maier-Stocker, Georg Niederalt, Johanna Loibl, Katharina Pielmeier, Claudia Bogner, Martina Müller-Schilling, Stephan Schmid
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15. First experience with the new generation of direct antiviral therapy for chronic HCV infection 2016 -2017, treated in a community hospital
Irina Alexandra Predescu, Andreas Lienig, Wolfram Zoller
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16. Intentional ingestion of sharp foreign objects: a case report and management recommendation
Vlad Pavel, Martina Müller-Schilling, Stephan A. Schmid
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17. Appendiceal stump bleeding - expect the unexpected
Daniel Popa [1,2], Mircea Ucenic[2], Cristina Rezi[1,2], Bogdan Fetica[3], Manuela Pumnea[1,2]
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18. Ulcerative colitis - atypical endoscopic appearance
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19. Pancreatic panniculitis - a dermatological illness or an internistic pancreatic disease? A case report
Patricia Mester, Georg Peschel, Killian Weigand, Martina Müller-Schilling
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20. Ultrasound diagnosis in chronic pancreatitis
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21. Is hyponatremia a negative prognostic factor in gastrointestinal pathologies?
Andreea Barbulescu, Ioan Sporea, Raluca Lupusoru, Damaris Pop, Corina Pienar, Laura Olariu, Iulia Ratiu
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22. How to induce constipation in experimental settings?
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23. A trip to India with side effects
Florian Berreth, Wolfram G. Zoller
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24. Video Capsule Endoscopy: quality assessment in a maximum-care hospital.
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Smoking is a risk factor for the development of esophago-respiratory fistula in esophageal cancer: a case control study

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Background: The development of esophago-respiratory fistula (ERF) in esophageal cancer (EC) is a devastating complication, leading to poor survival rates and low quality of life. The risk factors leading to ERF are only scarcely understood.

Methods: We were able to identify 47 patients with malignant ERF formation in EC in a period of 10 years. In a first step, we compared this group with 47 randomly selected patients with EC without ERF. In a second step, all 43 patients with squamous cell carcinoma (SCC) and ERF were matched in a 1:2 case-control fashion for primary tumor localization.

Results: Identifiable risk factors in EC patients were histology of SCC (P = 0.008), primary tumor localization in the upper esophagus (P < 0.001) and former or current smoking status (P = 0.003). Not associated with ERF formation were sex, age, TNM-stage, grading, length of the primary tumor and history of former or current tumor besides EC. An additional risk factor in SCC patients was age. Patients with ERF formation in SCC (median 63 years) were significantly younger than patients without ERF (median 67 years, P = 0.039). The "hot spot" for ERF formation was tumor growth 20-25cm distal to dental arch. More tumors with ERF formation showed growth in this segment, compared to tumors of patients without ERF.

Conclusion: Smoking is a previously not identified risk factor for ERF formation in EC.

Statin use and premalignant gastric lesions in patients with chronic cardiovascular diseases

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Background: 3-hydroxy-3-methylglutaryl-coenzime A reductase inhibitors, also known as "statins", are used to lower cholesterol levels and prevent atherosclerosis. Statins are also known to reduce the incidence of different types of cancers, such as lung, prostate or colorectal cancer due to their anti-inflammatory and immunomodulatory effects. **Aim**: To determine whether statins offer a protective effect against developing premalignant lesions such as glandular atrophy, intestinal metaplasia and dysplasia in patients with a background of premalignant risk factors exposure.

Methods: A series of 564 patients who underwent upper endoscopic examination for dyspeptic symptoms or anemia were recruited. We analyzed the correlation between statin use, *Helicobacter pylori* infection, and premalignant gastric lesions in patients with (n = 222; 53%-males) or without (n = 344; 44%-males) undergoing statin treatment. We registered the demographical data, drug exposure, symptoms, smoking, alcohol consumption, and other comorbidities. A total number of 295 patients received chronic treatment with proton pump inhibitors (PPI) due to previous gastric pathology or chronic gastrotoxic medication.

Results: A prevalence of 39.5% premalignant gastric lesions was registered in our study group, i.e. 26.4% gastric atrophy, 18.7% intestinal metaplasia and 0.7% dysplasia. In the multivariate logistic regression analysis, we noticed the protective role of statins (p=0.006; OR:0.59; 95% CI:0.40-0.86) against premalignant lesions in patients with risk factors exposure, represented by smoking (p=0.001; OR:1.99; 95% CI: 1.17-3.39) and age over 50 years (p=0.00; OR:3.09; 95% CI: 1-84-5.21). Meanwhile, statins proved to have no protective effect against other risk factors such as salty food diet (p=0.42), chronic alcohol consumption (p=0.18) or *H. pylori* infection (p=0.35). Chronic aspirin consumption, used for cardiovascular prevention, showed no protective effect against premalignant lesions (p=0.08), and long term PPI use was not associated with an increased incidence of premalignant lesions (p=0.23) in our study group.

Conclusions: In the studied population, statin treatment appears to reduce the incidence of premalignant lesions in smokers and patients over 50 years old, regardless of their gender or the use of other chronic medication.

Differences of spleen and liver stiffness between alcoholic liver disease and HCV hepatitis: a cross sectional analysis and response to treatment

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Background: Spleen stiffness (SS) in combination with liver stiffness (LS) has been shown to predict portal hypertension and its complications. However, it remains unclear whether the side of inflammation (lobular vs portal) affects the ratio of liver and spleen stiffness in alcoholic liver disease (ALD) and chronic HCV hepatitis and how it responds to therapeutic interventions. **Aim**: Cross sectional analysis of liver and spleen stiffness in patients with ALD and HCV hepatitis and their response to alcohol detoxification and HCV treatment.

Patients and Methods: We prospectively assessed LS and SS (Fibroscan, Echosens, Paris) in 98 patients with ALD and 137 patients with HCV hepatitis both before and 7 days after alcohol withdrawal or 4 weeks of HCV direct acting antiviral treatment. In addition, we performed routine lab parameters and ultrasonography.

Results: Using XL and M probe, LS could be assessed in 100% and SS in 80.4 % of patients. Despite lower mean LS in HCV (15.4 vs 25.3 kPa), SS was significantly higher in HCV as compared to ALD (45.4 vs 29.2 kPa, P<0.0001, see Table I). Spleen stiffness was still higher in HCV (47.7 vs 31.2 kPa) when HCV and ALD patients were matched for LS. These findings were also mirrored by the liver and spleen size. While livers were larger in ALD (15.9 and 13.9 cm, P<0.0001), spleen size was higher in HCV (14.1 vs 10.4, P<0.0001). Consequently, the ratio of SS to Liver stiffness was significantly higher in HCV than in ALD (3.9 vs 1.6, P<0.0001). LS significantly decreased after treatment in both diseases by comparable scale (-4.6 vs -4.9 kPa, P<0.0001). The decrease of LS correlated best with the resolution of GOT levels (r=0.65, P<0.0001). Spleen stiffness also decreased in both diseases upon treatment not reaching levels of significance in the rather short observation interval during alcohol withdrawal (see Table I). Notably, the SS to LS ratio did not change significantly during interventions in both diseases.

Conclusion: We here demonstrate that portal liver diseases such as HCV have an almost three times higher SS/LS ratio as compared to lobular-pronounced ALD. Our findings have important implications for the diagnosis of liver diseases.

Table I. Liver stiffness (LS) and spleen stiffness (SS) in patients with alcoholic liver disease (ALD) vs. chronic HCV hepatitis

Parameter	Group	Before	After	Delta	P value
AST (IU/L)	ALD	104	56	-51	<0.005
	HCV	56	26	-29	<0.001
ALT (IU/L)	ALD	63	51	-13	<0.0002
	HCV	61	25	-36	<0.001
Liver Stiffness (kPa)	ALD	25.3	21.7	-4.6	<0.0001
	HCV	15.4	10.4	-4.9	<0.0001
Spleen Stiffness (kPa)	ALD	29.2	26	-4.1	=0.18
	HCV	45.4	26.1	-19.2	<0.00001
Matched group Spleen Stiffness (kPa)	ALD	31.2	25.5	-5.7	=0.22
	HCV	47.7	28.9	-19.6	<0.00001
SS/LS ratio	ALD	1.6	1.3	-0.3	=0.2
	HCV	3.9	3.1	-0.8	<0.001

Low lysophosphatidylcholine levels may predict severe alcoholic hepatitis

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Background: Severe alcoholic hepatitis (SAH) remains a condition which results in high mortality and morbidity, as well as high healthcare costs. That is why adequate selection of patients who would benefit the most from corticotherapy is of the utmost importance. Although serum biomarkers are available (Maddrey Discriminant Function - MDF), the diagnosis of SAH relies on liver biopsy. Previous metabolomic studies have shown a core metabolic phenotype represented by decreased serum lysophosphatidylcholines (LPC) and increased serum bile acids that occur relatively early in liver diseases regardless of etiology, and remains stable in their evolution, including liver cirrhosis and hepato/cholangiocarcinoma. Our previous work also showed that decreased LPC levels are associated with alcoholic liver disease (ALD). **Aim**: The aim of the study was to assess the metabolic profile of patients with ALD and to identify potential new biomarkers associated with severity.

Methodology: Between December 2015 and September 2016, 64 patients with biopsy proven AH were included (38 with SAH - MDF≥32 and 24 with non-severe AH - MDF <32).

Fasting serum was stored at -80 degrees after centrifugation at 5000 rpm for 10 minutes. Specific purification protocol metabolomic analysis was performed using Thermo Scientific UHPLC UltiMate 3000 system, equipped with a Dionex quaternary pump delivery system and a Bruker Daltonics MaXis Impact MS detection equipment (version 2012).

Biostatistical analysis: the chromatograms obtained were processed using the CompassDataAnalysis_4.2 software (Bruker, Germany) and about 3000-4000 molecular masses were identified. Those data were further processed using ProfileAnalysis (Bruker, Daltonics): time alignment, normalization by sum of bucket values in analysis, 80% bucket filter, internal recalibration, etc. The matrix obtained

was further processed by MetaboAnalysis, to analyze samples through univariate and multivariate statistical analysis.

Results: Univariate and multivariate statistical analysis by MetaboAnalysis identified 10 potential biomarkers. Among them, LPC (18:0) showed good discrimination for SAH (AUC=0.804) with significantly lower values as compared with non-severe AH (0.38 fold change, p=6x10-11).

Conclusion: Severe AH appears to have a different metabolic profile, mainly due to changes in lysophosphatidylcholine metabolism. Targeted metabolomic studies are required in order to confirm the results and to evaluate the possible applications in current clinical practice.

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Liver stiffness values using 2d-SWE-Toshiba in healthy subjects

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Aim: To determine liver stiffness values in healthy subjects, by means of a new 2D-SWE technique from Toshiba, implemented on the Aplio I900 system.

Method: 43 subjects were included in the study (75.6% women, 24.4% men, average BMI=23.6 kg/m^2, mean age=38 years) with a normal abdominal ultrasound and without any known liver disease, in whom liver stiffness (LS) was evaluated using a 2D-SWE from Toshiba. Reliable LS measurements were defined as the median value of ten measurements acquired in a homogeneous area avoiding large vessels and with an IQR/median < 30%.

Results: Out of the 43 subjects, reliable LS measurements were obtained in 41 subjects (95.3%) by means of the 2D-SWE-Toshiba. The mean liver stiffness values in healthy subjects was 4.5 ± 0.7 kPa, CI 95% (4.2-4.7). There were no significant differences between the mean liver stiffness in men vs. women 4.6 ± 0.5 kPa, CI 95% (4.2 - 4.9) vs. 4.4 ± 0.7 kPa CI 95% (4.2 – 4.7) (p=0.26).

Conclusion: 2D-SWE-Toshiba has a very good feasibility in healthy subjects. The mean liver stiffness value determined by 2D-SWE-Toshiba in our cohort was 4.5 ± 0.7 kPa.

The value of ElastPQ to rule in and rule out HCV liver cirrhosis

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Aim: To evaluate the diagnostic performance of a point shear wave elastography using ARFI technique – ElastPQ, to rule in and rule out HCV liver cirrhosis, using Transient Elastography (TE) as the reference method.

Method: We included 209 consecutive subjects with HCV compensated chronic liver disease, in whom liver stiffness was evaluated in the same session by means of two elastographic measurements: TE (FibroScan, EchoSens) and ElastPQ (Affinity, Philips). Reliable LS measurements by TE (M or XL probe) were considered the median value of 10 LS measurements with a success rate ≥ 60% and an interquartile range <30% and for ElastPQ the median value of 10 LS measurements and an interquartile range <30%. To discriminate between various stages of fibrosis by TE we used the following cut-off values: F ≥2 : 7.1 kPa, F=4 : 12.5 kPa.

Results: Valid LS measurements were obtained in 93.7% (196/209) cases by means of TE and in 95.2% (199/209) cases with ElastPQ (p=0.64). In the final analysis 199 patients were included. Based on TE cut-off values we divided our cohort into 3 groups: F≤2: 38/199 (18.5%), F2-F3: 34/199 (17.5%), F=4: 127/199 (64%). The best cut-off value for discriminating liver cirrhosis (F4) was 10 kPa with an AUROC of 0.96, Sensitivity of 87.9, Specificity of 92.9, Positive Predictive Value(PPV) of 95.6 and Negative Predictive Value (NPV) of 81.5. There was a strong correlation between the measurements obtained by Transient Elastography and ElastPQ (r = 0.84, p < 0.001).

Conclusion: ElastPQ seems a reliable method to accurately diagnose patients with HCV liver cirrhosis. The best ElastPQ cut-off value for HCV liver cirrhosis (F=4) was 10 kPa with good PPV and NPV.

Diagnostic accuracy of three non-invasive methods to evaluate fibrosis in patients with HCV compensated liver cirrhosis

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Background and Aim: Non-invasive methods used to evaluate liver fibrosis may be elastographic or serologic. The aim of the study was to determine the diagnostic accuracy of three non-invasive methods to assess liver fibrosis: VTQ (Virtual Touch Quantification), TE (Transient Elastography) and the serologic method FibroTest (Biopredictive) in a group of patients with hepatitis C virus (HCV) compensated liver cirrhosis.

Method: A retrospective study was conducted which included 102 HCV-compensated cirrhotic patients evaluated in our department during 2016-2017. In these patients, the diagnosis of cirrhosis was established based on clinical, biological, and ultrasound criteria. For the diagnosis of liver cirrhosis, using non-invasive methods, we used the following cut-off values: TE ≥ 12 kPa, VTQ ≥ 1.81 m / s, and for FibroTest values ≥ 0.75. The patients were evaluated in the same session by TE (FibroScan, EchoSens), Virtual Touch Quantification [(VTQ) -Acuson S2000, Siemens]; in every patient 10 measurements were performed for each method and median values were calculated. In the same session blood samples were collected for FibroTest assessment.

Results: the study group included 68 (67%) women and 34 (33%) men, mean age 61 ± 8 years. Transient elastography correctly diagnosed 94 patients out of 102 (92%), FibroTest correctly diagnosed 83 patients out of 102 (81%), while VTQ correctly diagnosed 81 out of 102 (79%) patients. Transient elastography performed significantly better than VTQ (92.1% versus 79.4%, p = 0.04) and than FibroTest (92.1% versus 81.3%, p = 0.0005). There was no significant difference between the diagnostic accuracy of VTQ and FibroTest (p = 0.76).

Conclusion: Transient elastography had the highest diagnostic accuracy to diagnose liver cirrhosis in our study group (92%), and the other methods had an accuracy of 79% (VTQ) and 81% (FibroTest), respectively.

The value of ElastPQ and thrombocytes count for predicting presence of high risk varices

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Background and Aim: Ultrasound based elastographic methods and biological markers can be used as noninvasive tools for predicting the presence of high risk varices (HRV) in patients with advanced chronic liver disease. The aim of the study was to determine the utility of liver stiffness (LS) values measured by ElastPQ and thrombocytes count as non-invasive markers for prediction of high risk varices in patients with advanced chronic liver disease .

Method: In a retrospective study we included 61 subjects, 39 (63.9%) females and 22 (36.1%) males, mean age of 59.16 ± 8.67 years with advanced liver disease who underwent both liver stiffness measurements (LSM) with a pSWE technique-ElastPQ and upper gastrointestinal endoscopy. Reliable LSMs were defined as the median value of 10 measurements acquired in a homogeneous area and an interquartile range/median (IQR/M) <0.30. We defined as subjects with advanced liver disease those who had ElastPQ > 7 kPa and diagnosed as HRV grade II, III esophageal and gastric varices.

Results: We obtained reliable LSM in 60/61 subjects (98.3%): 27/60 (45 %) subjects had HRV, while 33/60 (55%) had no or first grade esophageal varices. The mean LS values for patients with HRV were significantly higher as compared to those with first grade or no varices (24.71 ± 16.99 kPa vs. 16.36 ± 7.82 kPa with p=0.0145). Regarding the thrombocyte count, the mean value for subjects with HRV was significantly lower than the value obtained for subjects without HRV (96,740 ± 56,128 vs. 15,5848 ± 90,508, p= 0.0045). The best LS cut-off value performed with ElastPQ for predicting the presence of HRV in our study group was: 11.96 kPa (AUROC 0.67; sensitivity 96.3%; specificity 39.3%; PPV 56.6%; NPV 92.9%). The thrombocytes cut-off value for the identification of patients with HRV was < 126,000 (AUROC 0.70; sensitivity 81.4%, specificity 57.5%; PPV 61.1%; NPV 79.2%).

Conclusion: The LS cut-off value of 11.96 kPa assessed by means of ElastPQ and the level of thrombocytes < 126,000 may identify subjects with HRV.

Bacterial infections and antibiotic spectrum in cirrhotic patients

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Background and Aims: One of the main causes of hospitalization and death in cirrhotic patients is bacterial infection. The management of these patients should be done rapidly and adequately by giving the proper antibiotic treatment, taking into account the local antibiotic resistance. The aim of the present study was to assess the most frequent bacterial infections, the pathogenic agent involved and the antibiotic spectrum in a cohort of cirrhotic patients.

Methods: We retrospectively analyzed 281 cirrhotic patients (mean age 62.7 ± 1.1 years, 58.4% men, 41.6% women) with bacterial infections, hospitalized in the gastroenterology department of a tertiary emergency hospital during 2016-2017. A complete workup (paracentesis, urine sediment, chest X-ray, and/or blood, ascitic fluid, and/or urine cultures) was performed at admission if the patients were decompensated and also whenever they deteriorated clinically during hospitalization.

Results: In our cohort, the most frequent infection was urinary tract infection representing 39.2% (110 /281) of all, followed by respiratory tract infections 22% (62/281), spontaneous bacterial peritonitis 21.7% (61/281), soft tissue infections 10% (28/281) and pseudomembranous colitis 7.1% (20/281). The major causative agents for urinary tract infections and respiratory tract infections were gram negative bacteria: *Escherichia coli* (60%), *Klebsiella pneumoniae* (15%), whereas *Enterococcus faecalis* and *Staphylococcus aureus* were found in 21%, and anaerobic agents in 4% of the cases. The main antibiotic resistance in urinary tract infections caused by *Escherichia coli* was found for beta-lactamase inhibitors followed by quinolones (Ciprofloxacin), while in the respiratory tract infections, *Klebsiella pneumoniae* was

sensible to quinolones, third generation cephalosporins and carbapenems.

Conclusion: The most frequent infections in our cohort of cirrhotic patients were urinary tract infections. The main resistance was to beta-lactamase inhibitors followed by quinolones.

Contrast enhanced versus conventional ultrasound guided liver biopsy in the diagnosis of hepatocellular carcinoma: A prospective study

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Background and Aims: Hepatocellular carcinoma (HCC) is the only major cancer in which diagnosis is not regularly established by histology. However, there are several circumstances where liver biopsy is recommended. Unfortunately, the sensitivity of ultrasound guided liver biopsy (USLB) is less than 80% and a negative biopsy does not rule out malignancy. Contrast enhanced ultrasound (CEUS) is an excellent method for both diagnostic and intervention procedures. The aim of this study was to evaluate the diagnostic accuracy of CEUS guided liver biopsy (CEUSLB) versus USLB in cirrhotic patients with focal liver lesions (FLL).

Method: A total number of 152 cirrhotic patients with either inconclusive FLL on CT or candidates for Sorafenib therapy were evaluated for inclusion in the study. Eight patients refused to sign the informed consent. The remaining 144 patients were randomly divided into two groups: a group who underwent CEUSLB (79 patients, 149 lesions) and another one who underwent USLB (65 patients, 122 lesions). The pathologic diagnosis was considered definitive if the biopsy showed malignancy. If the initial biopsy result was benign or negative for malignancy, then the result was either confirmed or denied based on CT, MRI, or clinical follow-up over a period of 6-12 months.

Results: In the CEUSLB group, 96.2% of the lesions were malignant (55 HCC, 15 cholangiocarcinomas and 2 metastases) compared to 96.9% (56 HCC, 5 cholangiocarcinomas, 1 lymphoma and 1 metastasis) in the USLB group ($p > 0.05$). There were no differences in tumor size between the two groups: 69.59 ± 35.75 mm in USLB compared to 74.84 ±34.90 mm in the CEUSLB ($p = 0.38$). The diagnostic accuracy was significantly higher in the CEUSLB group than in the USLB group (94.93% vs 73.38%, respectively; $p < 0.001$). On subgroup analysis, the sensitivity of CEUSLB compared to USLB was higher for both poorly visible tumors (92% vs 64%; $p = 0.006$) and tumors larger than 5 cm (95% vs 74%; $p = 0.01$), respectively. No major complications occurred in our patients except for hemoperitoneum in one case of the USLB group.

Conclusion: The use of contrast agents in guiding liver biopsy improved the diagnostic accuracy of the procedure especially in poorly visible tumors and large tumors by providing important intralesional information for differentiating viable, denaturalized, or necrotic tissue.

Diagnostic accuracy of contrast-enhanced ultrasound algorithm (ACR CEUS LI-RADSv 2016) for the diagnosis of hepatocellular carcinoma in patients with chronic liver disease

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Aim: This study aimed to test the latest approved version of a contrast-enhanced ultrasound algorithm (ACR CEUS LI-RADSv 2016) for detecting hepatocellular carcinoma (HCC), in a real-life cohort of high-risk patients.

Methods: We re-evaluated the CEUS studies of 298 focal liver lesions in patients at high-risk for HCC (liver cirrhosis of any etiology, chronic hepatitis B or C, with severe fibrosis, current or prior HCC) using the ACR CEUS LI-RADSv 2016 algorithm.

CEUS LI-RADS categories used for the diagnosis of HCC were: CEUS LR-5 (definitely HCC), CEUS LR-5V (HCC with macrovascular invasion), CEUS LR-TR (treated HCC).

Contrast-enhanced CT, contrast-enhanced MRI or histology were used as reference methods to evaluate the CEUS LI-RADS classification of the 298 lesions.

Results: According to the reference method, the 298 lesions were classified as follows (Table I): 211 HCCs, 60 non-HCC-non-malignant lesions (fatty infiltration, hemangiomas, simple cysts, regenerative nodules) and 27 non-HCC malignant lesions (liver metastases, cholangiocarcinoma, indeterminate).

Table I. Classification of the 298 lesions according to CEUS LI-RADS as compared to results obtained by the reference method.

CEUS LI-RADS Catergories	N	HCC	Non HCC/ Non malignant	Non HCC, Malignant lesions
LR1 definitely benign	20	0	20	0
LR2 probably benign	8	0	8	0
LR3 intermediate probability for HCC	23	9	13	1
LR4 probably HCC	76	59	13	4
LR5 definitely HCC	141	138	0	3
LR 5V macrovascular invasion	0	0	0	0
LR M definitely or probably malignant, not specific for HCC	30	5	6	19
LR TR (treated)	0	0	0	0
Total	298	211	60	27

The accuracy of ACR CEUS LI-RADSv 2016 for the diagnosis of HCC was 74.4%. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 65.4%, 96.5%, 97.8% and 53.5%, respectively.

When we used CEUS alone, a conclusive diagnosis of HCC was obtained in 69.6% of the cases (147/211), and using the algorithm in 65.4% of all HCCs (138/211) (p=0.35).

Conclusion: In our study, 65.4% of HCCs (138/211) were correctly diagnosed using the ACR CEUS LI-RADSv 2016 algorithm, which showed good sensitivity, excellent specificity and PPV for the diagnosis of HCC.

Multiparametric Ultrasound algorithm for the reevaluation of inconclusive focal liver lesions evaluated by contrast enhanced ultrasound

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Background and Aim: The new features implemented in ultrasonography have created the concept of multiparametric ultrasound (MPUS) [1], which can add valuable information to standard ultrasound evaluation. The aim of this paper was to evaluate the benefit of MPUS to the inconclusive focal liver lesions (FLLs) evaluated by means of contrast-enhance ultrasonography (CEUS).

Method: A three-step algorithm was designed. In the first step, an elastographic method was used that ruled in or out severe liver fibrosis (fibrosis ≥F3). The second step consisted of quantifying the tissue perfusion of the lesions evaluated by CEUS. This feature allows through the time intensity curve, the quantitative assessment of perfusion parameters in the late phase in comparison with the adjacent parenchyma, enabling the highlighting of the wash-out. In the third step with the help of a color-coded map based on perfusion kinetics (parametric imaging feature from GE-LOGIQ E9), the lesions were evaluated according to a parametric imaging map during the arterial phase, displaying by colors the enhancing pattern and the hyper-and hypo-enhanced areas of a FLL. We reevaluated according to the MPUS algorithm 70 inconclusive CEUS video-clips performed in our center, in which the final diagnosis was established by CT, MRI or by liver biopsy.

Results: We selected the raw data of 70 randomly, inconclusive CEUS examinations of FLLs over a period of two years (January 2015- December 2016) and reevaluated the CEUS video clips applying the MPUS algorithm. From 70 FLLs, 14 were not suitable for the algorithm due to inappropriate examination. From the remaining 56 FLLs, 29 (51.7%) were correctly diagnosed in concordance with the reference method; in 18 (32.1%) lesions a final diagnosis could not be established and in 9 (16%) cases the MPUS algorithm misdiagnosed the lesions. The predominant lesion was hepatocellular carcinoma (HCC), 22/56 (39.2%) cases. With the help of MPUS, we correctly diagnosed 17/22 HCCs.

Conclusion: With the help of our MPUS algorithm, we managed to orientate the diagnosis in more than 50 per cent of the lesions and established a correct diagnosis in 51.7%. An algorithm approach for the diagnosis of HCC seems to be a suitable method.

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Sphingolipids – new biomarkers for the detection of early and intermediate hepatocellular carcinoma

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Background and Aim: Throughout the last years metabolomics has played an important role in providing new insights into the detection and progression of hepatocellular carcinoma (HCC). Sphingolipids, a family of membrane lipids, are involved in numerous cell functions, including cell death pathways and have an altered expression in many types of cancer. The aim of this study was to identify a metabolomic biomarker for HCC diagnosis and to compare its diagnostic accuracy with that of alpha fetoprotein (AFP).

Method: 104 patients (54 HCC BCLC stages 0, A and B developed on compensated cirrhosis and 50 compensated cirrhotic controls) were included. Common workup for the assessment of liver disease and AFP was carried out in each patient. High pressure liquid chromatography (HPLC) coupled with quadruple time of flight electrospray in a positive ionization mode mass spectrometry (QTOF-ESI+-MS) was performed from serum samples of each patient. MetaboAnalysis, performing univariate and multivariate statistical analysis was used to identify candidate biomarkers. Their performance for detection of early/intermediate HCC was evaluated using semi-quantitative assessment and through a leave-one-out cross-validation based on area under the receiver operating characteristics (ROC) curve.

Results: 15 metabolites were identified. Sphingolipids are the most upregulated in HCC patients, particularly C16 sphinganine (C16-SPH) (p 0.001 vs. compensated cirrhosis). The expression of C16- SPH was 4.869 times higher in HCC than in cirrhotic controls (p <0.005)

The area under the curve (AUC) of C16-SPH for the diagnosis of HCC was significantly higher compared to AFP [0.969 (95%CI, 0.923-1) vs. 0.544 (95%CI, 0.415-0.673), p (deLong test) <0.001. For a cutoff value of 0.737, C16-SPH correctly classified 97/104 (93.26%) of patients.

Conclusion: Sphingolipids show a significant upregulation in patients with HCC compared to patients with cirrhosis. Of them, C16-SPH might stand as a novel diagnostic marker for the identification of early and intermediate HCC in patients with chronic liver diseases.

Delirium – of outstanding relevance for the interprofessional team in an intensive care unit with the focus on hepatology

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Background and Aim: Delirium increasingly gains relevance as an important comorbidity in intensive care medicine. Studies regarding delirium were carried out mainly in surgical intensive care units (ICUs). There are few data about delirium in the medical ICU. In our interprofessional observational study we attempted to analyze the incidence, causes and consequences of delirium in a medical ICU specialized in hepatology.

Methods: Patients admitted to the ICU of Internal Medicine I of the University Hospital Regensburg between March 2017 and August 2017 were screened in three steps daily, based on a new developed standardized questionnaire. The degree of sedation was determined using the RASS-Score. The patients with adequate vigilance were evaluated for delirium using CAM-ICU. Finally, there were other parameters included, especially the main diagnosis, hospitalization time in the ICU, medication, laboratory tests, medical history and alcohol consumption.

Results: 165 patients with adequate vigilance were examined using CAM-ICU. Delirium was diagnosed in 27% of patients: 40% of patients had a hypoactive form, 51% a mixed form and 9% a hyperactive form of delirium. The patients developed delirium after a mean time of 3.7 days hospitalization in the ICU and the delirium lasted on average 4.9 days. The mean hospitalization time of 19 days was massively increased. The delirium was best recognized through interprofessional teamwork. The positive predictive value of the team assessment was 83%. The emergency department (ED) is also an important unit for recognizing patients with delirium; 47% of the patients who developed delirium were admitted to the ICU through the ED, and the delirium was already recognized in the ED. A routine screening test for delirium in the ED has an outstanding value in the early recognition and therapy of delirium.

Conclusions: The first results of the observational study show the great relevance of delirium in an ICU focusing on hepatology. Cirrhosis is an important risk factor in developing delirium; alcohol abuse leads to a further increase of the risk. Delirium is best recognized in interprofessional teamwork. An additional daily screening test for delirium is important, since 40% of patients have a hypoactive, difficult to recognize form of delirium.

Intentional ingestion of sharp foreign objects: a case report and management recommendation

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Introduction: Foreign body (FB) ingestion is a common clinical problem. Patients with increased risk include children and geriatric patients, intellectually or mentally disabled people, patients with psychiatric disorders or prisoners. About 80-90% of ingested blunt foreign bodies pass through the gastrointestinal (GI) tract without symptoms, impaction or mucosal injury. However, 10% to 20% of the ingested FBs, especially sharp-pointed objects, batteries or magnets, require endoscopic removal, and 1% or less of the patients require further surgical interventions in case of complications. Endoscopic removal provides high efficacy with considerable low interventional risks using protective devices such as endoscopic overtubes to remove sharp-pointed objects. Laparoscopic or open surgery is the last resort when other techniques have failed.

Case report: A 18 year old female with borderline personality disorder (BPD) was admitted to the emergency department having swallowed three razor blades, three pinboard tacks and several pieces of broken glass. After the orotracheal intubation for airway protection interventional gastroscopy was performed at the intensive care unit. To protect the esophagus from injury by sharp-pointed objects we used a specialized overtube (Guardus® Overtube, US Endoscopy, 25 cm). Endoscopically, all foreign bodies were removed. A CT scan confirmed that the gastrointestinal tract was empty of other FBs. After 12 hours of monitoring, the patient was extubated and transferred to the psychiatry department.

Discussion and Conclusion: Intentional ingestion of foreign objects is a topic that has generated mounting interest among medical professionals over the past two decades. Foreign body ingestion has been reported in patients with personality disorders as part of a spectrum of self-harming behavior. Most FB ingestions involve sharp objects. Management of FB ingestion in patients with BPD requires high levels of interdisciplinary collaboration between gastroenterologists, psychiatrists and surgeons. Endoscopic removal is the first choice in the management algorithm of this clinical emergency due to its efficacy, low morbidity, and low cost compared to

surgical treatment. The timing of intervention is influenced by the patient's age and clinical condition, the size, sharpness and type of the ingested object as well as anatomic location of the lodged object. Orotracheal intubation of the patients before endoscopy is recommended as well as the use of a specialized removal device.

Appendiceal stump bleeding - expect the unexpected

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Introduction: Lower gastrointestinal bleeding (LGIB) is a frequent cause of hospital admission, triggered by a variety of etiologies. Appendiceal hemorrhage is an extremely rare cause of LGIB. The reported causes of appendiceal bleeding include erosions and ulcers, acute appendicitis, angiodysplasia, diverticulum, endometriosis, lymphoma, gastrointestinal stromal and carcinoid tumors, Crohn`s disease and tuberculous appendicitis, aortoappendiceal fistulae, intussusceptions, post appendectomy stump granuloma bleeding and Dieulafoy lesions. Herein, we report the case of appendiceal stump hemorrhage, in a patient with appendectomy performed 23 years ago, successfully treated by open assisted laparoscopy completion appendectomy.

Case report: A 47-year-old male, with an appendectomy performed before 23 years, was admitted in our service for hematochezia, started 1 day before (3 episodes of hematochezia in total), without any other associated symptoms. Upon admission, the patient was hemodynamically stable, had no fever, the abdomen was not painful upon palpation, and the clinical examination was within normal limits; hemoglobin (Hb) was 12.5 g/dl with no out other significant biologic changes. We decided to perform a colonoscopy. Bowel Preparation Scale (BBPS) was 4. Ileoscopy showed regular appearance throughout the last 5 cm, fresh blood was detected in a small amount at the cecum and ascending colon, also fresh blood and small clots at the level of the sigmoid and rectum, which were rigorously removed through washing without detecting a bleeding source. Due to the poor preparation, we decided to continue the preparation and reexamine the patient the subsequent morning: preparation was BBPS 9, ileoscopy on the last 7 cm showed normal appearance, no lesions revealed, and no traces of fresh blood or clots.

In order to eliminate the possible source of bleeding in the small intestine, we performed a videocapsule endoscopy. In real time imaging, we noticed a large amount of fresh blood at the colon level, therefore the examination was prematurely interrupted and, after having visualized the recording, we noticed that the blood appeared at the time of the capsule crossing through the ileocecal valve on to the cecum, without any indices of lesions or blood at the level of the stomach or small intestine.

Considering a possible Dieulafoy lesion, we immediately performed a colonoscopy; this time, fresh blood and clots were found on the entire colon but especially at the level of the cecum and ascending colon. After washing and aspiration, we revealed a small diverticulum at ascending colon level with a clot at orifice level, without active bleeding; we injected adrenaline 1/10000 around the orifice and two metallic clips were mounted. A CT angiography scan with contrast was performed but the source of the hemorrhage was not identified.

Having a Hb level of 9.3 g/dl, the patient received volemic resuscitation and perfusable iron solutions, and remained hemodynamically stable, with an increasing Hb, no signs of haematochezia. On the third day after clamping, he had another massive haematochezia, and Hb decreased to 7.6 g/dl. The patient was informed about a possible "life saving" surgical intervention, but first another colonoscopy was attempted to identify the source of bleeding. At the level of the cecum and ascending colon, a small amount of fresh blood and several small clots were seen, and at the level of the appendiceal orifice we identified an adhering clot, removed with relative opposition. We gently advanced with the colonoscope through the appendiceal orifice and found in the appendiceal stum, a bluish, millimetric lesion, possibly a vessel without active bleeding, and non approachable for endoscopic therapy.

The patient was scheduled for surgical intervention for the following day and an appendiceal stump of approximately 2-2.5 cm was revealed, so a completion appendectomy was performed.

The patient's recovery was uneventful and he was released from the hospital the 3rd day after surgery. He no longer presented episodes of haematochezia after the intervention.

Histopathology exam revealed a 2mm area of ulceration at the level of the appendiceal stump and a surface blood clot without any malignancy signs.

Conclusion: Most LGIBs stop spontaneously and in 5% the cause of bleeding will remain unknown. Appendiceal hemorrhage is an extremely rare cause of LGIB: 40 cases have been reported and only 1 case of appendiceal stump bleeding However, the gastrointestinal endoscopist should bear in mind this possible cause even in the setting of a previous appendectomy.

Ulcerative colitis - atypical endoscopic appearance

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Aim: To report a case of ulcerative colitis severe form, with atypical endoscopic aspect at initial diagnosis.

Case report: We present a 21 year old female, diagnosed during pregnancy (24 weeks) with severe iron deficiency anaemia (Hb 4g/dl) corrected with blood transfusions, and

with noninvestigated recurrent episodes of bloody diarrhea. After delivery, she presented with colicky abdominal pain, bloody diarrhea (3-4/day) and important weight loss.

On admission the physical examination revealed: intense pallor, malnutrition, BMI 15kg/m^2, stable vital signs, tachycardia, no fever, tender abdomen but no guarding, no palpable mass, audible bowel sounds. Laboratory tests showed iron deficiency anaemia (Hb 10.5g/dl), thrombocytosis, moderate inflammatory syndrome (CRP 3.77mg/dl) , hypoalbuminemia, hypokalemia, hypocalcemia, negative stool culture. Rectosigmoidoscopy evidenced no vascular pattern, high friability, multiple ulcerations (Mayo score 3), and pseudopolyps (max size 15 mm). Progression beyond 30 cm from the anal verge was considered unsafe.

We performed also an upper digestive endoscopy which evidenced surprising findings. The first and second part of the duodenum had important erythema, friability, multiple small ulcerations. The stomach had also multiple corporeal erosions. Biopsies were taken. Neither AINS use nor *Helicobacter pylori* infection were recorded.

The histopathological examination of the duodenal mucosa revealed diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, active inflammation causing cryptitis and crypt abscesses.

We initiated corticotherapy, associated with oral and topical Mesalamine followed by major clinical improvement, but every attempt to reduce the steroids dosage less than 10 mg was associated with relapse, after 1 year of progression. Biologic treatment was considered, but the patient's follow-up was interrupted because she left the country.

Conclusion: Although rare, diffuse gastroduodenitis resembling ulcerative colitis with respect to macro- and microscopic findings occurs in patients with ulcerative colitis. It was described associated with severe forms postcolectomy, especially in young patients, and could be a marker of poor prognosis.

Pancreatic panniculitis - a dermatological illness or an internistic pancreatic disease? A case report.

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Introduction: Pancreatic panniculitis is a rare disease characterized by large subcutaneous fat necrosis. It is reported in 2-3% of all patients with acute pancreatitis. The pathophysiology is supposed to be dominated by local activation of pancreatic enzymes, such as lipase or alpha-amylase.

Case report: A 68-year-old patient without evidence of acute or chronic pancreatitis was admitted at the emergency room because of red, painful spots on the lower leg. At the time of admission, laboratory tests showed significantly elevated serum lipase, up to 11,130 U/l, and highly increased inflammatory parameters (C reactive protein). However, systemic therapy with prednisolone did not reveal any positive effect on the dermal lesions. The nodules were biopsied, and the histopathological diagnosis of pancreatic panniculits was established. Endosonography and CT-scan however did not show any signs of acute or chronic pancreatitis. Furthermore, IgG4-pancreatitis or vasculitis were excluded. FDG-PET-CT did not show signs for tumor lesions that could produce increased levels of pancreatic enzymes. We suspected immune reactivation within the context of the dermatological illness responsible for the elevated inflammation markers. Finally, we chose local therapy with cortisone.

Discussion and Conclusion: The pathogenesis of pancreatic panniculitis remains unclear. Increased permeability and microcirculation are supposed to be induced by pancreatic enzymes such as trypsin. Therapy is always dependent on the underlying disease. Some studies have shown a correlation between acute/chronic pancreatitis, pancreatic cystic lesions and adenocarcinoma of the pancreas. However, we were not able to prove a pancreatic pathology at this time point, although pancreatic panniculitis is supposed to be specific for pancreatic diseases. As might be in our case, skin lesions can precede weeks or months before pancreatic disease becomes apparent.

Ultrasound diagnosis in chronic pancreatitis

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Background and Aim: Chronic pancreatitits is a potentially severe disease with a prevalence and incidence different according to geographic regions. Ultrasound is the main imaging technique used in the diagnosis of this disease. Diagnostic criteria are: the increased volume of the pancreas, changes in the pancreas echostructure and the presence of calcifications, cysts and dilatation of Wirsung`s duct. The sensitivity and specificity of standard transabdominal ultrasound for the diagnosis of chronic pancreatitis are 70%, respectively 90%. The aim of this study was to assess retrospectively the main aspects of chronic pancreatitis seen in standard ultrasound.

Methods: A retrospective study was performed including all patients with ultrasound- established diagnosis of chronic pancreatitis in a period of three years (2015-2017) in our tertiary Department of Gastroenterology and Hepatology. The inclusion criteria were: patients diagnosed in our department with chronic pancreatitis that were evaluated by ultrasound and/or computer tomography, Magnetic Resonance Imaging and ERCP.

The diagnosis of chronic pancreatits was confirmed by the presence of calcifications, cysts, enlarged size of the pancreas and dilatation of Wirsung`s duct on an imaging technique. Complications of chronic pancreatitis such as mechanical obstructions of the common bile duct were assessed.

Results: A total of 46 patients (13% female, 87% male, mean age 55±10 years) were included. A percentage of 93.5% of the cases had positive diagnostic elements (dilatation of Wirsung`s duct 54.3%, calcifications 30.4%, cysts 10%). In 30 patients, a second line imaging technique was performed. In 10 patients MRI investigation was performed, which confirmed in 90% cases our ultrasound diagnosis, while in 20 patients evaluated by CT, in 75% patients our ultrasound diagnosis was confirmed. As a complication, obstructive jaundice appeared in 28.3% patients, all diagnosed using standard ultrasound.

Conclusions: In our group of patients with chronic pancreatitis, 93.5% had positive diagnostic elements. Conventional ultrasound is a very accurate method as first line diagnostic method.

Is hyponatremia a negative prognostic factor in gastrointestinal pathologies?

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Background and Aim: Hyponatremia is the most frequent serum electrolyte disorder observed in institutionalized patients. The aim of this study was to find out whether hyponatremia can be used as a negative prognostic factor in some gastrointestinal pathologies.

Methods: We performed a retrospective study of a database of patients who were admitted to the Gastroenterology and Hepatology Department of the County Hospital of Timisoara, in a period of one year. We divided the patients into four groups: 1) liver cirrhosis, 2) acute cholangitis, 3) obstructive jaundice and 4) acute pancreatitis. From every group we included all the patients with hyponatremia and a control group with a normal value of serum natrium.

Results: A total of 242 patients were included in the study: 71 patients were diagnosed with acute cholangitis, 37 (52%) female, 20 (28%) had hyponatremia, mean age was 66.5±10.3 years. A group of 60 patients had liver cirrhosis, of whom 25 (35 %) were female; 30 of them (50 %) had hyponatremia and the mean age was 61.1±11.5 years. Regarding acute pancreatitis 60 patients were included, 19 (31.6 %) female, 30 (50%) had hyponatremia; the mean age of this group was 55.2±9.1 years. The last group of 51 patients was diagnosed with obstructive jaundice: 27 (52.9 %) female, 30 with hyponatremia, with a mean age of 67.2±8.3 years. We found significant statistical differences between hyponatremia and the severity of the disease in the group of patients with liver cirrhosis and acute cholangitis (p=0.05).

There were no significant differences between hyponatremia and the severity of the disease in the groups of patients with acute pancreatitis and obstructive jaundice.

Conclusion: Hyponatremia can be considered as a negative prognostic factor in patients with liver cirrhosis and in patients with acute cholangitis.

How to induce constipation in experimental settings?

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Background and Aims: Constipation is a very common condition with no perfect treatment yet. Therefore, experimentally-induced constipation could help in developing new drugs. We undertook a systematic review all of experimental models of constipation, in order to find out their benefits and disadvantages.

Methods: We searched for experimental models of constipation in the main international databases. We looked only for experiments in animals, mainly in rodents and dogs. Data were analyzed according to the methodology for systematic reviews.

Results: There are numerous experimental models. The most widely used models are based on opioids, while improvement was realized by L-glutamine, magnesium oxide, naloxegol, sildenafil, linaclotide and diet. Outcomes were bowel movements, number of fecal pellets, stool humidity, latency to the first defecation and mucin secretion. The biochemical markers used are guanosine-3',5'- cyclic monophosphate, immunoglobulin A, decrease of TNF alpha level and inhibition of 2,2-diphenyl-1-picrylhydrazyl radical.

Conclusions: Constipation may be induced experimentally to study physiopathology or evaluate laxative therapy. Several models are reliable and accessible to investigators.

A trip to India with side effects

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A 27-year-old man was admitted to our hospital with persistent bloody diarrhea and abdominal pain for more than 4 weeks. The year before he had been traveling in India for months.

Colonoscopy and ultrasound revealed ulcerative colitis as well as a large liver abscess, which was subsequently drained. Microbiology confirmed invasive amoebiasis as the underlying cause. The patient received Metronidazole for 10 days followed by Paromomycin for another 10 days and made a full recovery.

One year later the same patient returned to the hospital after a journey to South East Asia and India. He had acholic stool, jaundice and dark urine. Because of the fever and the cervical lymph node swelling malaria and Dengue had been excluded in Thailand. Liver enzymes were increased and PCR as well as serology tests were positive for Hepatitis E. The patient recovered without specific therapy.

Shortly after leaving the hospital he then caught high fever and headache. A renewed hospitalization was necessary. Blood cultures showed yet another infectious disease: Salmonella typhi. Based on the susceptibility testing the patient received Cefotaxim intravenously and again made a full recovery. Up to this day he remains well and continues to travel.

This case illustrates the importance of a thorough medical history in the returning traveler as well as the regional spectrum of infectious diseases.

Video Capsule Endoscopy: quality assessment in a maximum-care hospital

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Since its introduction in 2000, small bowel video capsule endoscopy (SBVCE) has quickly become the first-line imaging modality for many small bowel pathologies. However, a high standard in procedural quality is necessary in order to legitimate this important role in patient care.

In our maximum-care centre approximately fifty SBVCE are performed annually. Using data of the last two years, capsule endoscopies were evaluated for quality indicators as well as general parameters (age, gender, passage time).

In total, 101 SBVCE were performed in 2016 und 2017. The patient's mean age was 64.2 years (range: 16 to 92), mean small bowel transit time was 4.87 hours (range: 0.41 to 11.22). Main indications to perform SBVCE were suspected small bowel bleeding (82.2%), Crohn's disease with suspected small bowel involvement (6.9%), suspected small bowel tumour (5.0%) and suspected coeliac disease (1.0%).

Quality indicators in general showed good or acceptable performance in procedural quality: there were no cases of capsule retention, and complete visualisation of the small bowel was documented by passage into the colon in 86.1 % of cases. However, only 25.7% of SBVCE showed findings relevant to the main clinical question. This suggests that indication and timing of capsule SBVCE need to be examined more closely.