



# Second Internist

Gastroenterohepatology meeting with  
**International Participation**

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# Abstract Book





# Obesity in nonalcoholic fatty liver disease

*Dr. Biljana Ivanovska Bojadjiev, specialist in internal medicine, subspecialist in endocrinology*

Obesity is on the rise globally due to poor lifestyle choices, such as high-energy diets and insufficient physical activity, leading to a variety of metabolic disorders. One significant consequence is Metabolic-Associated Fatty Liver Disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), which affects over 30% of the global population and is now recognized as the leading cause of chronic liver disease worldwide.

MAFLD represents the liver's response to metabolic syndrome, characterized by central obesity, insulin resistance, hypertension, and dyslipidemia. This condition has a bidirectional relationship with other metabolic disorders, significantly complicating patient outcomes. Factors contributing to MAFLD include genetic predispositions, insulin resistance, and changes in gut microbiota, which encourage hepatic fat accumulation and impede insulin function in the liver.

Professional bodies like the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend screening for MAFLD in individuals with obesity, metabolic syndrome, or diabetes using non-invasive methods such as the NAFLD fibrosis score or transient elastography to assess liver fibrosis risk.

Effective management of MAFLD revolves around lifestyle modifications aimed at achieving a minimum of 5% weight loss, supplemented by appropriate pharmacotherapy when necessary. Therapies like pioglitazone and GLP-1 receptor agonists are endorsed for specific patient groups, demonstrating benefits in managing insulin resistance and reducing liver fibrosis. Conversely, metformin is not recommended for NASH treatment despite its use in diabetes management.

Surgical options, including bariatric surgery, also play a role in severe cases by significantly improving metabolic profiles and supporting long-term weight management, positioning them as valuable strategies in MAFLD treatment.





# MASLD in prediabetes and diabetes

*Irfan Ahmeti, Macedonia*

Nonalcoholic fatty liver disease (NAFLD) is a fatty liver disease that occurs with fat accumulation, inflammation, and fibrotic changes in the liver. If not recognized in the early stages, it can progress to the more severe stages of liver disease. Lately, this has been replaced by the term metabolic-associated steatohepatic disease (MASLD) as a whole term for long-standing steatotic liver disease for a severe one cardiometabolic risk of associated insulin resistance (such as prediabetes, type 2 diabetes, atherogenic dyslipidemia or hypertension) without to have a cause of steatosis. The main symptoms of MASLD are commonly associated with obesity and diabetes and can progress if these conditions are not well controlled or if they are not treated and managed appropriately. Progression leads to metabolic dysfunction-associated steatohepatitis (MASH, formerly known as nonalcoholic steatohepatitis or NASH), There is no cure for MASLD or MASH. and control of associated factors is a vital part of the progression of liver damage. Diabetes is a major risk factor for the development of NASH, disease progression to cirrhosis, and HCC. Recent studies in US patients have estimated that NAFLD is prevalent in >70% of people with type 2. Management of MASLD is aimed at progression to more severe stages. Lifestyle intervention, weight reduction, new drugs such as GLP-1 agonists, pioglitazone are used in people with MASLD.





# Insulin Resistance, obesity and MAFLD (case report)

*Andrea Veljanovska Stojanovski, Aleksandar Manolev, Biljana Ivanovska Bojadjiev, Miroslav Boshkovski, Elena Perkova, Olivera Gjorgieva Janev*

Obesity is a chronic disease with complex pathophysiology, defined by excessive fat deposits. Associated with increased risk of T2DM, increased CV risk. MAFLD is one of the complication od obesity.

Young man 37 age was referred to us suspected for liver damage, increased insulin 62.6, FPG = 5.2, HOMA-IR 15.3, cholesterol 5.5, TGR 2.34, LDL 3.53, HDL 1.02, non-HDL 4.48, AST 89, ALT 120, ALP 59.8, GGT 42.9. According to his lab.tests the FIB-4 Score was 1.45, that lead us to further investigations - US of liver with grade 3 of liver steatosis. Liver 2SWE elastography was performed with a mean value of elasticity of 7-8kPa. We did a total body compound with started measures (weight 117 kg, height 177 cm, BMI = 37.3 -class 2). The scan showed composition of total fat mass 45.187 % (concentrated of the trunk), lean tissue 63.446%. Related skeletal muscle index(RSMI) 10.3 kg/m<sup>2</sup>. A fully program was designed - physical activity walking/riding bike 150 min/week + 3 times anaerobic exercises and 1800 kcal diet. The goal was achieving min.7% reduction of body weight. After 3 mounts we didn't achieve our goal, so we reduced the diet on 1600 kcal/day and increased the physical activity on 300 min/week.

After 3 mounts (6 mounts after starting the program) we still didn't achieve our goal, so we decided to start pharmacology treatment with GLP1-RA(Liraglutide) with titration to maintenance dose of 3mg. After 6 mounts we have achieved 7% weight reduction.

Corrections were made with the lipid status. The patient can't be scored with SCORE2 (<40 years)

Control laboratory findings were insulin 24, FPG 4.9, HOMA-IR 5.2, cholesterol 4.9, TGR 1.68, LDL 2.9, HDL 1.23, non-HDL 3.67, AST 32, ALT 53, Tr 312 Fib-4 score 0.52

Weight loss can prevent metabolic and CV complications. When lifestyle changes don't make the willing achievement, the pharmaco-therapy for obesity is recommended.

With pharmacotherapy we can expect maximum 12-15% weight loss.

**Key words:** obesity, hyperinsulinemia, MAFLD, lipids, lifestyle changes, GLP1-RA





# Contemporary approach in management of dyslipidemia in liver steatosis

A. Manolev, M. Boshkovski, B. Ivanovska-Bojadjiev, E. Perkova, O. Gjorgjieva-Janev

Non-alcoholic-fatty-liver-disease (NAFLD)-associated with T2DM, hypertension and dyslipidemia - hepatic manifestation of metabolic syndrome. NAFLD - fatal/non-fatal-CVD risk factor - atherogenic dyslipidemia (plasma hypertriglyceridemia, increased VLDL, IDL, LDL, low levels of HDL-c). Dyslipidemia in NAFLD - pure hypercholesterolemia, hypertriglyceridemia and combined dyslipidemia. Subclinical atherosclerosis in ~70%men and 45%women with NAFLD.

Principles for managing dyslipidemia in NAFLD:

1. Diagnosis/phenotyping of dyslipidemia (tot-cholesterol, LDL-c, non-HDL-c, HDL-c, triglycerides, ApoB- in high triglyceride, DM, obesity, metabolic syndrome, very low LDL-c, Lp(a) at least once in lifetime.
2. Individual ASCVD risk-assessment - SCORE2/SCORE2-OP - 10-year-risk of fatal/nonfatal CVD, risk factors - documented manifestations of ASCVD, blood pressure, smoking history, T1DM or T2DM, overweight/ obesity, chronic kidney disease (CKD), family history of premature CVD (men<55y, women< 60y) and genetic lipid disorders.
3. Target values for lipids - NAFLD+moderate CVD-risk, LDL-c<2.6mmol/L; NAFLD+high CVD-risk, LDL- c reduction $\geq$ 50% or LDL-c<1.8 mmol/L, NAFLD+very CVD high risk, LDL-c reduction $\geq$ 50% or LDL-c<1.4mmol/L.
4. Lifestyle modification: Weight reduction - target BMI 20-25kg/m<sup>2</sup>, waist circumference men<94cm and women<80cm. A weight-reduction $\geq$ 5% - significant improvement in hepatic steatosis,  $\geq$ 7%-improvement in hepatic inflammation/resolution of NASH,  $\geq$ 10%-improvement in hepatic fibrosis. LDL-c reduction 0.2mmol/L for every 10kg weight loss. 5%-weight-reduction lowers triglyceride~10%. 150-200min/week of moderate-intensity aerobic-physical activity in 3-5sessions. Diet - Mediterranean diet. Daily alcohol intake - reduced/completely avoided in hypertriglyceridemia, advanced fibrosis( $\geq$  F2).





## 5. Pharmacotherapy:

Hypercholesterolemia - Statins - major role in primary and secondary CVD prevention, safe in patients with NAFLD (transaminase elevations  $<3 \times$  upper limit), compensated cirrhosis, still underutilized - fear of hepatotoxicity, beneficial pleotropic effects, reduce NASH and reduce risk of liver fibrosis. Ezetimibe - LDL-c reduction  $\sim 65\%$  using high-intensity-statin+ezetimibe. PCSK9 inhibitor - secondary/primary prevention for very-high-CVD-risk.

- \* Hypertriglyceridemia - considered in high-risk (triglycerides  $>2.3$  mmol/l), statins are first-line-drug, reduce triglycerides 15–30%. Omega-3-fatty-acids in combination with statin reduce 30–50% triglycerides, additional treatment with fenofibrate/bezafibrate.
- \* Bempedoic acid, Inclisiran, Lanifibranor, GLP-1RA, SGLT2i - effects in NAFLD, obesity and dyslipidemia.

Patients with NAFLD and dyslipidemia have significant ASCVD risk, screening programs are urgently needed and aggressive treatment of dyslipidemia plays key role in primary/secondary ASCVD prevention.





# MAFLD in young patient with obesity and hypercholesterolemia – case report

*Miroslav Boshkovski, Aleksandar Manolev, Biljana Ivanovska Bojadziev, Elena Perkova, Andrea Veljanovska Stojanovski, Olivera Gjorgieva Janev*

Introduction: Every patient with NAFLD and obesity should be screened for MAFLD. Female patient, 40 years old, with sedentary lifestyle, obesity class 1 - BMI=33.9, TH=170 cm, TW=98 kg, with history for NAFLD > 8 years with increased hepatic enzymes and dyslipidemia. At the first exam BP=120/70 mmHg, HR=78/min, normal ECG. Abdominal US showed grade 3 of liver steatosis, US FLI>5 (liver-kidney contrast-severe (3); area of focal sparing (1); posterior attenuation of ultrasound beam (1); difficult visualization of the gallbladder wall (1)). Laboratory analyses showed glucose 5.5 mmol/L, HbA1c 5.6 %, Total Cholesterol=5,5 mmol/L; LDL=3,5 mmol/L; HDL=1,2 mmol/L; Triglycerides=1,3 mmol/L; AST=66; ALT=112; PLT= 362; Fib 4= 0,75; creatinine 98, eGFR 79ml/min.

The patient diagnosis were: Steatotic liver disease - (SLD); Obesity class 1 (MASLD); Dyslipidaemia with phenotype: hypercholesterolemia and no confirmation for pre-diabetes or diabetes and no conclusion for Metabolic Syndrom. The SCORE 2 risk stratification for non-fatal and fatal CVD was done with score <2,5% (low to moderate CVD risk).

We suggested weight reduction with dietary life style changes and increased physical activity.

After 15-months on the control examination her parameters were TH=170 cm; TW=83 kg; BMI=28,9 - she lowered 14% of TW and now she was overweight patient, not obese. Laboratory analyses were: Total Cholesterol=5,6 mmol/L; LDL=3,6 mmol/L; HDL=1,2 mmol/L; Triglycerides=1,4 mmol/L; AST=27; ALT=44 - normal hepatic enzymes. On the US findings we had mild steatosis and US FLI >3<5 (liver-kidney contrast-mild/moderate (2); area of focal sparing (1); no posterior attenuation of ultrasound beam (0); difficult visualization of the gallbladder wall (absent) (0)).

We had still nonregulated lipids, with hypercholesterolemia phenotype, so we decided to add statin treatment - Rosuvastatin 10mg once a day and continue with dietary life style changes with increased physical activity.

After 6-months the results were: Total Cholesterol=3,6 mmol/L; LDL=2,4 mmol/L; HDL=1,1 mmol/L; Triglycerides=1,4 mmol/L; AST=28; ALT=36.

Conclusion: With right method of diagnosing, monitoring and treatment, we achieved excellent results on lipids control, MAFLD and weight reduction.

Keywords: obesity, MAFLD, dyslipidemia, lifestyle-changes







# MAFLD in patient with obesity and T2DM

*Elena Perkova, Andrea Veljanovska Stojanovski, Aleksandar Manolev, Biljana Ivanovska Bojadziev, Miroslav Boshkovski, Olivera Gjorgieva Janev*

Introduction: Every patient with T2DM and obesity should be screened for MAFLD  
Patient on 44 years, smoker, married, with sedentary lifestyle, BMI=33.9, visceral obesity, increased hepatic enzymes, HTA, T2DM(Metformin 2x850 mg), dyslipidemia. At the first exam BP=140/90 mmHg, HR=88 b/min, normal ECG. Abdominal US showed grade 3 of liver steatosis. On 2SWE with average value in 8 measury points of 7 kPa.Doppler of carotids showed dynamic ordered spectrum. Control lab analyses showed Insulin 24.8, glucose 11.8, HbA1c8.9 %, HOMA-IR 13, Chol 4,3, Trg 2,2, LDL 2.3, HDL 0,98, non-HDL 3.32 (with statin therapy), AST 58, ALT 106, Tr 213, creatinine 107, eGFR 76ml/min, TSH 4.64. We suggested triple OAT (Metformin 2x1000mg +Vidagliptin 2x50 mg+Gliclazide 3 mg) and weight reduction, exercise, low salt intake (that he didn't practice). 8-months later he had increased hepatic enzymes, FIB-4 score 1.46 (AST 103, ALT 164, PLT 243), glucose 9.8, HbA1C 8.2% Chol 4.5, Trg 2,32, LDL 2.5, HDL 0,89, non-HDL 3,31, creatinine 123, urea 4,5, eGFR 64ml/min, UACR 48 mg/g. Control ultrasound was the same. We performed 2SWE with average value in 12 measury points of 7 kPa, that leads to steato-fibrosis stage 2. Color Doppler with satisfactory RI(6-6.2). We switched the therapy to dual statin therapy (Rosuvastatin/Ezetimibe) and SGLT2-inh(Empagliflozin 25 mg) + Metformin (2g). 6-mounds after, the hepatic enzymes decreased, but still high AST 62, ALT 98, Tr 239, Fib- 4 score 1.15, FPG 7.6 mmol/L, HbA1c7.9 %, Chol 3.93, Trg 1,47, LDL 2.2, HDL 1,02, non-HDL 2.9, creatinine 96, eGFR 86ml/min, UACR 27 mg/g. Still nonregulated diabetes, we decided to add GLP1-RA(oral Semaglutide). After 6-mounds the results were AST 22, ALT 48, Tr 264, Fib- 4 score 0.53, FPG 6.8 mmol/L, HbA1c 6.7 %, Chol 3,62, Trg 1.33, LDL 1.7, HDL 1.33, non-HDL 3.32, creatinine 83, eGFR 103ml/min, UACR 20 mg/g  
With right method of diagnosing, monitoring and treatment, we achieved excellent results with diabetes control, lipid status, MAFLD and renal function.  
Keywords: obesity, MAFLD, hypertension, dyslipidemia, lifestyle-changes





# Noninvasive biomarkers in assessment of CLD

*Paolo Montalto, Italy*

Chronic liver diseases constitute a highly concerning and growing disease burden, in particular the rise in metabolic syndrome with MASLD represents the real pandemic jeopardizing the sustainability of our society.

Chronic liver disease tend to go unnoticed; the clinical onset is often a dramatic event (i.e variceal bleeding) in people unaware to be chronically ill.

It is essential to raise awareness and to effectively stratify the risk in general population.

Liver biopsy has been the gold standard for staging fibrosis, but it has many limitations, and there is an increasingly need of alternative non-invasive tools (NITs).

Serological markers (both «indirect» and «direct») are particularly helpful in ruling out disease, selecting people to be referred to liver clinic among general population: Fib-4 test (age, AST, ALT, Platelet Count) is the best triaging tool.

The advent of Liver Stiffness Measurement (LSM) by transient elastography (TE) in the early 2000s marked the beginning of a new era both in fibrosis and in steatosis grading in CLD, and NITs became increasingly key aspects in Baveno Consensus Conference.

LSM by TE powered by CAP is able to identify «at risk MASH patients» and holds also prognostic value identifying patients having advanced disease, still in asymptomatic phase (compensated Advanced Chroni Liver Disease; cACLD), and those having CSPH. Combined with Plt Count LSM by TE allows to rule out high risk varices, avoid unnecessary endoscopy.

Finally spleen stiffness measurement with specific probe has been proposed as a new marker and it correlates with the size of oesophageal varices and HVPG.





# cACLD - The importance of multidisciplinary approach

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Over the past few decades, the prevalence of advanced chronic liver diseases (ACLD) has risen and is expected to further rise given the change in epidemiological and etiological factors. The availability and growing widespread use of non-invasive testing contributed to diagnosis of ACLD at an earlier stage. An ongoing chronic liver injury without appropriate assessment and management in the asymptomatic phase will lead to deteriorated liver function. The variations in outcomes in patients with ACLD are tightly related to the access of adequate healthcare and good outpatient management is crucial. Preventing decompensation and hospital admission will allow for improved quality of life for patients with ACLD.

Compensated ACLD (cACLD) is the asymptomatic phase of ACLD with absence of gastroesophageal variceal bleeding, ascites and/or hepatic encephalopathy. This phase encompasses two stages of cACLD based on the presence or absence of clinically significant portal hypertension (CSPH). The development of CSPH is the turning point in ACLD which further determines the occurrence of complications. The presence or absence of CSPH is associated with different outcomes and risk of death and consequently different diagnostic and therapeutic interventions are needed depending on the stage.

Adequate management of cACLD implies a multidisciplinary approach and team working including clinicians caring for patients with ACLD in secondary and tertiary care facilities, nurses, nutritionists and surgeons. The patient itself should be well informed on his condition and actively involved in decisions regarding his management as his understanding of the impact of lifestyle, screening and primary prophylaxis of variceal bleeding will largely contribute to better outcomes.

**Keywords:** advanced chronic liver disease, compensated liver cirrhosis, portal hypertension





# Utility of US in complex liver guided interventions

*Aleksandar Gjoreski - Acibadem Sistina, Macedonia*

The Utilization of ultrasound(US) in everyday interventional radiology and hepato-gastroenterology practices is becoming more and more available. In this presentation I will try to emphasize and to touch briefly all the variety of US guided minimally invasive procedure that can be carried out in a comprehensive interventional radiology unit.

We will speak of the importance of good ultrasound knowledge, and why ultrasound can be more efficient than CT, fluoro or MRI guidance. In the next part we will start with the most simple US guided liver procedures, but one of the most important and definitely the most frequent ones, biopsies. I will try to explain the different types of biopsies and biopsy equipment for liver through cases from our everyday practice.

In the next part of the lesson we shall move to US guided liver drainages, and here we shall speak about the percutaneous treatment of simple liver cysts with aspiration, drainage and sclerotherapy and then we shall move on with percutaneous drainage of liver hydatid cysts and liver abscesses.

Next, I will speak about US guided puncture of biliary ducts during the access in percutaneous biliary drainage and stenting procedures.

Next I will focus on percutaneous ablative procedures in the liver like RF ablation, MW ablation and cryoablation which is a minimally invasive curative treatment of primary and secondary liver tumors and I will show the advantages of the new techniques like fusion imaging guidance during ablation.

In the last part of the presentation I will briefly mention some of the new possibilities of US in liver lymphangiography and the real time US guided puncture of the portal vein system during TIPS placement, and also portal vein puncture during pre-operative portal vein embolization.





# Population Screening for Liver Fibrosis and Cirrhosis

*Prof. Ivica Grgurevic MD PhD FRCP (Lon)  
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The increasing global burden of chronic liver diseases (CLD) necessitates effective strategies for early detection and management. Liver fibrosis, a critical determinant of prognosis in CLD, often progresses silently until advanced stages, underscoring the need for population-based screening.

Chronic liver diseases account for significant mortality, with 2 million deaths annually, making it the 11th leading cause of death worldwide. Key risk factors include high alcohol consumption, non-alcoholic fatty liver disease (NAFLD), and viral hepatitis. In the European Union, lifestyle factors such as obesity and alcohol consumption contribute significantly to the prevalence of CLD.

This presentation outlines the criteria for CLD screening, emphasizing non-invasive diagnostic tests like elastography and specific blood tests (e.g., FIB-4, ELF). The FIB-4 index, despite its ease of use, shows limitations in accuracy, particularly in populations with risk factors such as diabetes and obesity. Combining FIB-4 with ELF tests can reduce false positives and unnecessary referrals, enhancing the diagnostic process.

The Liver Risk Score, incorporating variables such as age, sex, fasting glucose, and liver enzyme levels, offers a promising tool for stratifying risk and predicting liver-related mortality. Studies suggest that a significant proportion of the population could benefit from initial screening with non-invasive methods, followed by more specific tests for those with elevated risk markers.

In conclusion, the integration of non-invasive diagnostic tests and stratified screening protocols could substantially improve the early detection and management of liver fibrosis, ultimately reducing the burden of advanced liver disease. Ongoing research and large-scale studies will continue to refine these screening strategies, aiming to implement practical solutions in healthcare systems globally.





# US Differentiation of Primary and Secondary Focal Liver Lesions

*Mirjana Brvar, Department of Radiology, Maribor University Medical Centre, Slovenia*

Ultrasound (US) is usually the first imaging method used in the diagnosis of focal liver lesions. Depending on clinical and laboratory data, it may simply be the screening procedure for the detection of possible focal lesions.

Frequently, focal liver lesions are found incidentally during abdominal US examinations for other reasons. In such cases, the correct algorithm in the characterization of the so-called "incidentalomas" is very important. A multiparametric approach is suggested for the characterization of focal liver lesions.

In my presentation, the B-mode US, doppler, and contrast-enhanced US characteristics of various benign lesions (cysts, fluid collections, regenerative nodules, FNH, focal fatty sparing, focal liver infiltration, hemangiomas, adenomas...) and malignant lesions (hypo- and hypervascular metastases, hepatocellular carcinoma, cholangio-carcinoma...) will be discussed. The importance of determining the echogenicity of the rest of the liver parenchyma and the patency of the liver vessels will also be explained (steatotic liver, fibrotic liver, congestion, thrombosis...).





# Ultrasound fusion with CT and MRI in hepatal lesions

*Prof. Gordana Ivanac, University Hospital Dubrava, University of Zagreb, School of Medicine*

Ultrasound fusion simultaneous use different imaging modalities which enable maximum use of advantages of each specific indication for hybrid exam (fusion). Ultrasound can be simultaneously performed with MSCT, MR and PET examinations.

Diagnostic ultrasound fusion is used primarily for lesions that cannot be sonographically differentiated, and are visualized on MSCT, MR or PET images and can be used in lesions of unknown etiology for additional sonographic evaluation. Except standard B-mode ultrasound the other ultrasound modalities can be utilized: doppler analysis, sonoelastography, contrast ultrasound (CEUS) with morphology analysis of vascularization.

Fusion of imaging modalities is implemented in modern ultrasound scanners. Except for diagnostic purposes, ultrasound fusion is used also in interventional radiology for the purpose of treatment and guidance during subcutaneous interventions like drainages and radiofrequency ablation.

Advantages include visualization in real-time without using ionizing radiation and acceptable price. Disadvantages are low contrast resolution in comparison with MDCT and MR examinations, narrow field of view, artefacts from present air and fat tissue and respiratory movements.





# Dopler ultrasound in liver transplantation

*Ivica Sjekavica*

In liver transplantation, dopler ultrasound is the first method in preoperative treatment of patients, intraoperative confirmation of vascular anastomosis patency, and postoperative monitoring with an emphasis on detection of complications. Perihepatal abdominal accumulations of fluid can be hematomas, ascites, abscess formations, as well as pleural effusions.

Complications with transplanted liver are divided into vascular, biliary and parenchymal. The most important vascular complications are on the hepatic artery, such as thrombosis leading to graft deterioration, hepatic artery stenosis, a-v fistula and pseudoaneurysm. Complications of the portal vein and caval anastomosis include thrombosis and stenosis, as well as pseudoaneurysms of the portal vein anastomosis more often in children. Biliary complications are obstructions and strictures of anastomosis, bile leakage with the formation of biloma and lithiasis.

Graft rejection is the most common parenchymal complication, but also the most common complication of all in liver transplantation.







# Therapeutic approach in CSPH and cirrhosis

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**Introduction:** On 17.06.2021, 48-years old. woman, comes for an examination at our health facility, with complaints of: weakness, loss of appetite, loss of body weight, has lost about 10 kg in the last few months, with occasional frequent bowel movements, without admixtures of mucus and blood, in visibly relatively poor general health. History of comorbidities: HTA, Non-smoker, No\_history of allergies.

**Objectives:** Multidisciplinary approach and management for early detection and treatment of the disease.

**Material and methods:** Abdominal ultrasound, Laboratory analyses, ECG, X-ray, CT of the abdomen with contrast, MRI, PET-Scan, surgical treatment.

**Results:** Abdominal echo performed at PZU "Echomedika"-Kochani: Stomach distention was noted, with an ectopically slightly thickened wall. A suspicious vaguely circumscribed, hyperechoic formation, on a broad base, was seen in the wall. Gastroscopy and contrast-enhanced abdominal CT indicated. Lab.\_resul.: 29.06.2021: SE-15/40; Le-6.9; er-3.18; Hgb-116; TBI-26.9; trig-0.81; HDL-1.47; CKI-59; alpi-56; ldi-188; HOL-4.4; ldl-2.6; fe-15; phos-1.41; AST-22; ALT-45; CRP-0.6; Mg-1.02; urea-4.6; gluc-4.9; GGT-31; CA-2.15; creat-43; F4-14.9 pmol/L; TSH-0.208 uIU/mL; ATA<10.0; H. Pylori, serum-0.89 IU/ml, feces-negative. Gastroscopy\_13.07.2021-PHI UC for Toxicology-Skopje: End Dg: Prolapsus\_via\_cardiae. Gastritis\_chr\_cum\_intestinalisatio\_susp. Pseudopolypus\_ventriculi\_pars\_proximalis\_c.minoris-par post\_cum\_ulceratio\_superficialis. Bulbitis chr. Histological finding: Well\_differeniated neuroendocrine tumor. PET scan 10.09.2021: Note: a well-differentiated tumor (gastrinoma) may be a low FDG avid neoplasm and the finding may be falsely negative. CT of abd. with contrast on: 28.10.2021 in PHI\_CH-Shtip: A multi-phase CT evaluation of the abdomen and pelvis was performed. The stomach was hypotonic with no visible mass. It is not well distended as it is not performed as a water dilated gastric exam. No free fluid is sent into the abdomen and small pelvis. On 04.03.2023 – Hospitalized and operated at PHI St.Naum Ohridski-Skopje, Dg. Gastrinoma ventriculi. PH finding: Intestinal metaplasia cum low gradeet high grade intraepithelial neoplasia. Angiodysplasia ventriculi.

**Conclusion:** The importance of the internist approach for early detection and treatment of neoplasms.





# Drug induced liver disease - are we aware enough?

*Niko Bekjarovski, University Clinic of Toxicology; Medical Faculty Skopje*

More than seventy year, pills are part of almost every home in our planet. In the period between 1950-2022 the average life expectancy grown up from 46,5 to 71,7 years. The quality of life dramatically moves forward, and pills and supplements have their own part in this. More than four thousands different drug formulation is approved as medicines. Almost all of these drugs have different side effects, and hepatotoxicity is probably the most common one.

The aim is to analyze clinical presentation, laboratory findings and therapeutic challenges of drug induced hepatotoxicity. Different pathological findings, laboratory disturbances, and diagnostic approaches of drug induced liver injures are evaluated. DILI protocol and classification and the treatment of liver injures are challenge in everyday practice. The use of N-acetyl cistine have a limited value in drug induced liver injures.

Drug induced hepatotoxicity will be growing medical problem, and have to be considered as a possible reason in any liver damages without clear diagnose.

**Key words:** drug, liver, toxicity





# Future therapeutic modalities in chronic liver diseases

*Dimitar Tonev, Bulgaria*

"This presentation will focus on the latest development in the most actively explored field in Chronic Liver Diseases, namely MASLD. The focus of the presentation will be on the current phase III and phase IIIb data with some emphasis on challenges and non-medical treatment at its current state.

Given the timeframe there will be a short description of the drug development conundrum in this important domain as well as latest regulatory wisdom and less emphasis of epidemiology, pathophysiology and clinical features of MASLD which is covered elsewhere in the program. "





# Diagnostic experience and follow up with fibro-scan in patients with viral hepatitis - our experience

*Marija Dimzova, Macedonia*

This presentation reviews our comprehensive experience using FibroScan® for diagnosing and monitoring liver fibrosis in patients with viral hepatitis at our institution. FibroScan®, a non-invasive transient elastography device, has revolutionized the management of patients with chronic hepatitis B (HBV) and hepatitis C (HCV) by providing a rapid, office-based assessment of liver stiffness, which is directly correlated with fibrosis stage.

Globally, HBV and HCV affect hundreds of millions, posing risks of cirrhosis and hepatocellular carcinoma (HCC). Current treatment goals focus on the suppression of HBV replication and achieving a sustained virological response in HCV to prevent disease progression. Traditionally, liver biopsy was the standard for evaluating liver fibrosis but had limitations due to its invasiveness and risk of complications.

Our institution's experience, drawing from a cohort of 109 patients with HBeAg-negative chronic HBV, highlighted the effectiveness of FibroScan® in providing a safer, more patient-friendly option with comparable accuracy. Most patients had liver stiffness measurements indicating mild to absent fibrosis, which is critical for guiding clinical management and treatment decisions.

FibroScan® results are reliable and reproducible, making it an excellent tool for both initial evaluation and follow-up in viral hepatitis patients. It allows for the non-invasive monitoring of disease progression or regression, facilitating timely adjustments in therapy.

This review underscores the transformative impact of FibroScan® on the diagnostic landscape of liver diseases, offering a paradigm shift from invasive procedures to a non-invasive, patient-centric approach.





# Therapeutic approach in cholestatic liver disease

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Cholestasis represents a state of impaired bile formation and/or impaired bile flow. Cholestasis can be caused by many different conditions, but in most cases, it develops in patients with some of the cholestatic liver diseases such as: Primary biliary cholangitis (PBC), Primary sclerosant cholangitis (PSC), IgG4-associated cholangitis (IAC), cholestatic Drug-induced liver injury (DILI), Ductopenia and vanishing bile duct syndrome (VBDS), Intrahepatic cholestasis of pregnancy (ICP) and in patients with some rare inherited cholestatic syndromes. Biochemically the cholestasis is defined by elevation of alkaline phosphatase (ALP) level higher than 2 times the upper limit of normal (ULN), elevation of Gamma-Glutamyl Transferase (GGT) higher than 3 times ULN followed by conjugated hyperbilirubinemia at more advanced stages. Regarding presentation, in early stage, the cholestasis can remain asymptomatic, but in most patients, it causes pruritus, fatigue and jaundices. The therapeutic options are addresses towards suppression of the underlying pathogenic process, towards treatment of the cholestasis-related symptoms, such as pruritus and towards management of complications that result from chronic cholestasis such as metabolic bone disease. Ursodeoxycholic acid (UDCA) is the first-line treatment options in patients with PBC, ICP, severe VBDS and it can be usefully in improving of symptoms in some patients with PSC. UDCA at a dose of 13-15 mg/kg per day has a beneficial effect on cholestasis-related symptoms, biochemical profile, histological findings, and in PBC patients, UDCA decreases disease progression and improves survival. In patients with intractable pruritus the stepwise treatment approach includes administration of cholestyramine, rifampin, naltrexone or sertraline. Additional supportive measures towards slowing down the disease progression include alcohol abstinence, avoidance of hepatotoxic drugs, maintenance of ideal body weight with appropriate diet and exercise, immunization according to recommendation and serologic status of the patient and expert hepatology consultation for long-term management, screening and surveillance.





# Liver and aging - new chapter in every day clinical practice

*Biljana Petreska Zovik, Macedonia*

Aging is one of the most important risk factors for the development of chronic diseases, such as cardiovascular diseases, diabetes mellitus, osteoporosis, neurodegenerative and malignant diseases. The mechanisms and hallmarks of aging and pathogenic mechanisms for these diseases are, in fact, largely overlapping.

The liver is an organ in which complex metabolic processes of essential importance for maintaining the homeostasis of the organism take place, through the regulation of energy metabolism, xenobiotic and endobiotic clearance and molecular biosynthesis. This is precisely why changes in liver function during aging also contribute to susceptibility to age-related diseases. For example, the liver regulates systemic energy metabolism through hepatic glucose and lipid homeostasis, steroid biosynthesis/degradation, and insulin signaling. This explains the beneficial effects of dietary interventions (such as caloric and protein restriction) on aging and age-related diseases. Dysregulation of hepatic energy metabolism, in turn, will lead to the development of various age-related pathological conditions, such as insulin resistance, diabetes mellitus and non-alcoholic steatosis of the liver (NAFLD), etc.

The aging process of the liver is mostly dependent on alterations and dysregulation of mitochondrial function leading to inflammation and cellular senescence. These changes cause phenotypic changes of all liver cells – hepatocytes, sinusoidal endothelial, stealth and Kupffer cells) and impairment of liver function. Of particular importance are changes in Liver Endothelial Sinusoidal Cells (LESC), which represent a significant unrecognized risk factor for the development of age-related cardiometabolic diseases, but also a potential therapeutic target for the prevention and treatment of these diseases.





# Current therapeutic strategies in acute variceal bleeding

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Variceal bleeding is a major complication of portal hypertension and represents a leading cause of death in patients with cirrhosis. Current available therapies achieve control of bleeding in about 80% of patients, but still 20% show either a failure to control the bleeding or an early recurrence of the hemorrhage in the first 6 wk after the initial bleeding.

Although diagnostic and therapeutic developments have led to a significant improvement in the prognosis of this complication mortality after an episode of acute variceal bleeding remains high and is in the range 15%-24%. Prognostic indicators after an episode of variceal bleeding likely to accurately predict outcome are severity of liver disease, quantified as Child-Pugh and Model for End-Stage Liver Disease (MELD) scores, active bleeding during endoscopy, hepatocellular carcinoma, bacterial infection, renal failure and hepatic vein pressure gradient > 20mmHg.

Initial resuscitation in acute variceal bleeding is aimed at maintaining an appropriate delivery of oxygen to the tissues. Optimal volume replacement aims maintaining systolic blood pressure around 100 mmHg and should be done with human albumin fraction or gelatin-based colloid. Blood transfusion should be aimed at maintaining hemoglobin at 70-80 g/L.

Endoscopy is the gold standard for the diagnosis of variceal hemorrhage and should be performed as soon as safely possible after admission. Hemostatic management is based on the combination of pharmacological and endoscopic therapy. For patients with uncontrollable bleeding second line treatment includes balloon tamponade, shunt procedures and esophageal stents. Up to 20% of cirrhotic patients who are hospitalized due to GI bleeding present with bacterial infections and an additional 50% will develop an infection while hospitalized.

Tense ascites increases portal pressure and should be treated with paracentesis along with albumin replacement when indicated. This has been shown to decrease portal and variceal pressure. Enteral feeding should be resumed as soon as a 24 h interval free of rebleeding has been achieved.





## A Quick Review of Barrett's Esophagus - First Experiences of Radiofrequency Ablation Treatment in Republic of Macedonia

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**INTRODUCTION:** Barrett's esophagus (BE), a condition when an abnormal intestinal-type epithelium with intestinal metaplasia (IM) replaces the stratified squamous epithelium that normally lines the distal esophagus, is associated with an increased risk of esophageal adenocarcinoma. Radiofrequency ablation (RFA) is an endoscopic treatment modality for eradication of BE. Primary circumferential ablation is performed using a balloon-based bipolar electrode, while secondary treatment of residual parts is performed using an endoscope-mounted bipolar sector electrode. RFA is a safe endoscopic ablation technique highly effective in removing BE with either low or high-grade dysplasia (LGD/HGD) and in preventing progression of disease. The actual appearance and detection rates of BE in North Macedonia (NM) are not yet well established.

**OBJECTIVE:** To analyze, the first experiences at the University Clinic of Gastroenterohepatology (UCG), using RFA in patients (pts) with BE with LGD or HGD, since this technique was introduced for the first time in NM, at our Institution in November 2021; to compare the last 4 year (2020-2023 [second period]) results with a first period from 2002-2008 concerning the appearance and detection rate of BE and to analyze the management process of BE pts in the last period, by assessing the time of diagnosis, presence of active reflux esophagitis (ARE) and other upper GI conditions, the cite of index endoscopy, rate of misclassification errors confusing short segment BE diagnosis with IM of the cardia (IMC) and gastro-esophageal junction (IMGEJ), Barrett's length (<3sm and >3sm), Prague classification use, adherence to biopsy protocol guidelines, number of histology evaluations per patient, number and time intervals of endoscopic controls if they're suggested, type of RFA used and number of sessions needed per patient to accomplish eradication, post-interventional therapy used and eventual side effects.

**MATERIAL AND METHODS:** North Macedonia is well defined area of examination and all of true BE pts certainly come to our Clinic since RFA is performed only at our Institution. In cross sectional retrospective analysis, the data were collected from 26 512 endoscopy records of pts managed at UCG in a period from 2002-2008, as well as those during 2020-2023 period (16 656 records) who underwent upper endoscopy and were recorded in "My appointment" national registry.







**RESULTS:** Unlike 2002-2008 period when there were 31 cases of BE recorded (average appearance and detection rate of 0.13), there was 3 times increment in the last 4 year period with the detection rate raised to 0.36 with appearance of 43 BE cases. The mean age of last period pts was lower compared to previous one (51.8 years vs. 58.8 years). Males were dominant in both periods (71% males from 2002-2008 and 74% from 2020-2023). We detect a bit of improvement through avoiding making the diagnosis during ARE with drop from 45 to 39% from 2008 to 2023. Index endoscopy with first endoscopic suspicion and biopsies were done at our Institution in most of the cases (72%). Analyzing the 43 BE patient's endoscopy records in correlation with histology findings during last period, it was found that true BE is present in only 25 (58%) pts, with rest of them (18) belonging to misclassification cases with IMC and IMGEJ. There were 9 long segment BE cases and 16 with short segment. Prague classification was used in 64% of cases with Prague scores ranking from C2M2 to C17M17. The determined adherence rate to Seattle biopsy protocol was 34%. At the time of index endoscopy 39 of 43 pts with endoscopic suspicion of BE received biopsy with histology examination comparing to 100% in true BE group (25pts) during follow-up endoscopies. The second histology expert exam was provided for all pts with true BE before diagnosis was definitely accepted. Most of them (14 pts [56%]) had LGD, following by 10 cases with IM and only 1 with HGD. The follow-up endoscopy was provided in 81% of cases, regardless of whether true BE was confirmed or not. The mean number of follow-up endoscopies was 7.1 per patient ranging from 1-10 in 4 year period, referring to excessively endoscopy follow-up practice in managing BE patients. The mean time elapsed since the diagnosis was made until recruitment in this study was 2.7 years in BE group. Among 15 pts treated with RFA with 28 sessions at all (average of 1.9 sessions per patient), 2 received therapy using circumferential RFA, 7 using focal RFA and 6 combined techniques. The BE eradication was endoscopically and histologically confirmed in 13 (87%) pts, 1 was counted for additional treatment and only 1 with confirmed flat HGD, concomitant peptic stricture and RFA treatment failure was send to surgery with unfavorable fatal outcome. All pts received double dose of PPI along with topical alginates and corticosteroids. No side effects from RFA were detected.





## CONCLUSIONS

The recognition of BE and its presence in Macedonia is on the rise. As the number of newly registered cases increases, the mean age of BE population decreases. Despite the Macedonian gastroenterologist's and pathologist's improvement in terms of avoiding endoscopic and histologic diagnosis within biopsies in presence of ARE, there is still lack of knowledge and training among Macedonian gastroenterologists and pathologists in order to be in concordance with ACG 2022 and ESGE 2023 recommendations, thus reducing the burden of false positive cases with unnecessary repeated endoscopies and misclassification errors towards clear distinction of BE from IMC and IMGEJ. Adherence to structured biopsy protocol for BE and use of Prague classification was unsatisfactory and needs further improvement. All of the pts with BE received review pathology confirmation before proceeding to RFA. LGD was most frequent among pts treated with RFA. Our results only confirmed well established fact, that RFA is associated with a high rate of complete eradication of both dysplasia and IM in BE and it is safe even when repeated for numerous times. Still, after the introduction of RFA in NM, we are witnessing unjustified approach to recommended endoscopic surveillance intervals based on degree of dysplasia and BE segment length that can be assumed as a consequence of two things, the insufficient endoscopy training and education and unjustified fears of general population.

**Key words:** Barrett's esophagus, radiofrequency ablation.





# Therapeutic approach in GERD

Gjorgjievska B. PZU D.med medical

Gastroesophageal reflux disease is a sensor motor disorder that is defined as a condition that develops when there is a return of contents from the stomach back into the esophagus. Anatomical abnormalities, such as a hiatal hernia, can worsen esophageal reflux. It is a very common disorder occurring between 10-30% in Western Europe and North America. In the United States, 42% of the adult population had GERD-associated symptoms.

Patients with GERD fall into three categories: Non-erosive reflux disease (NERD), Erosive esophagitis, Barrett's esophagus. Risk factors for the occurrence of GERD are smoking, alcohol, coffee, obesity, high-fat diets, intake of chocolates, peppermint, citrus juices, as well as the use of certain medications (narcotics, calcium channel blockers).

Several factors participate in the pathogenesis of the disease, such as: LES dysfunction, hiatal hernia, esophageal dysmotility, impaired esophageal defense mechanisms, hypersecretion of gastric acid, duodenogastroesophageal reflux, esophageal hypersensitivity, delayed gastric emptying, genetic factors. In the clinical presentation the symptoms are burning or burning behind the sternum, the presence of heartburn, nausea, belching, and as alarm symptoms in GERD are dysphagia, odynophagia, anorexia, weight loss, anemia, hematemesis.

Diagnosis is made by clinical presentation, X-ray of esophagus with barium mash, upper digestive endoscopy, esophageal pH monitoring, esophageal manometry, pH capsule, PPI test.

The therapeutic approach in GERD includes: confirmation of the diagnosis of GERD, adequate relief of GERD symptoms, treatment of erosive esophagitis if present, maintenance of mucosal healing, improvement of the patient's quality of life (reducing body weight, stopping smoking, raising head in bed, avoiding foods that lead to reflux symptoms.)

Drug treatment is started with PPIs or X2 receptor antagonists. If there is no adequate response, antacids and alginates, mucoprotectives and prokinetics can be added, and surgical and endoscopic interventional procedures are intended for people where medical treatment has no effect.

**Key words:** GERD, PPIs, H2 receptor antagonists





# Patient care in CLD

MILAN MISHKOVIKJ, MSc,

Hepar Centar, through innovative strategies and multi-stakeholder collaboration, is at the forefront of transforming liver health management in Macedonia and Europe. By fostering a strong patient movement and engaging with policy decision-makers, scientists, doctors, and the corporate industry, the organization seeks to elevate liver health on national and European agendas.

Key initiatives include launching multifaceted public awareness campaigns through social media, round table discussions, and educational materials focusing on fatty liver disease risks, symptoms, and consequences. Hepar Centar has also been pivotal in sharing personal stories from affected individuals, thereby humanizing the condition and promoting early diagnosis and intervention.

In the medical community, Hepar Centar has organized workshops and webinars to deepen healthcare providers' knowledge on liver diseases, advocating for early diagnosis and effective management. The formation of partnerships with medical associations, government agencies, and pharmaceutical companies has enabled a coordinated response to liver health challenges.

Significant milestones achieved include the establishment of the first National Declaration on Liver Cancer and the creation of a multidisciplinary liver unit center. This has facilitated enhanced policy advocacy, screening, and treatment protocols, with particular focus on eliminating hepatitis C virus (HCV), managing obesity, alcohol-related liver diseases, and addressing rare liver diseases.

The organization's efforts in integrating digital health technologies and health technology assessments (HTA) into liver health strategies underscore a commitment to innovative, cost-effective solutions that enhance patient outcomes and healthcare delivery across the region.

By embracing a holistic approach that includes patient advocacy, medical education, and international collaboration, Hepar Centar is setting new standards in liver health management, ensuring that no one is left behind in the fight against liver disease.





# Budd-Chiari Syndrome as a consequence of Essential thrombocythemia – a case report

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**Introduction:** Budd-Chiari syndrome is a rare and potentially life-threatening condition, that occurs as a result of partial or complete obstruction of hepatic venous outflow, and may involve one or more hepatic veins, the inferior vena cava or the right cardiac atrium.

**Case report:** We present a 46-year-old woman (D.B.), with intense abdominal pain, accompanied by nausea. A few years ago, the patient was diagnosed with Essential thrombocythemia (ET), with moderately elevated level of platelets, while the rest of the haemogram was normal. In addition, she has JAG 2 gene mutation. She had regular check-ups at the University Clinic of Hematology and was under regular prophylactic therapy with Aspirin 100mg. However, since a year ago, on her own initiative, she stopped the Aspirin therapy, as well as regular hematology tests. In her Town Hospital, native CT series of abdomen was performed, revealing findings of hepatomegaly, with dilatation of the left and the right portal branches, splenomegaly and perihepatic, perisplenic and interintestinal presence of free fluid ascit. There was no evidence of thrombus, but there was suspicion about its presence. The next day, another CT scan of abdomen was performed, this time with contrast, which revealed that the hepatic veins were not visualized, and there was substenosis of the inferior vena cava at the drain points of the hepatic veins, a finding that supports Budd-Chiari syndrome. Parenteral anticoagulant therapy was started immediately. It resulted with moderate improvement in middle and left hepatic vein flow.

**Conclusion:** Considering that the patient was diagnosed with Essential thrombocythemia, we believe that the discontinuation of Aspirin prophylaxis is one of the reasons for the development of Budd Chiari Sy and its consequences.

**Keywords:** Budd Chiari Sy, thrombosis, essential thrombocythemia.





# Prognostic and clinicopathological value of PD-L1 and HER2 in colorectal cancer

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**Objective:** The prognostic value of PD-L1 and HER2 in colorectal cancer is current subject in many studies, systematic reviews and meta-analysis. Our aim in this study is to evaluate the expression of PD-L1 and HER2 and to analyze the relationship with clinicopathological characteristics in metastatic colorectal carcinoma (mCRC).

**Materials and methods:** mCRC was diagnosed in 90 cases at Clinical Hospital Acibadem – Sistina and all were stained immunohistochemically with PD-L1 using clone SP263 and HER2 clone 4B5 in tissue microarray. The expression of PD-L1 was evaluated with different cut-offs of >1%, >10%, >50% of tumor cells. The expression of HER2 was evaluated as in gastric carcinoma with scores of 1+, 2+ and 3+.

**Results:** Positive expression of PD-L1 was evaluated in 17cases (18,8%). Ten were male patients and 7 were females. Eighty eight percent of the positive cases were patients with age more than 50 years. More than a half of positive cases (10) showed cut off >1%. Four percent of positive cases showed cut off >10% and all of them were located in rectosigmoid colon with stage IIIB and IIIC. Three cases were evaluated with a cut off >50% all of them G3 mCRC, stage IIIC and IVA, of which 2 cases were in right colon associated with BRAF mutations. There were 36 (40%) positive cases of HER2, of which 32 were with 2+, and 4 cases expressed 3+. Ten cases of HER positive cases were located in right colon and 26 mCRC were in left colon. Twelve HER2 positive cases(33%) had KRAS/NRAS mutations, 5(13%) had BRAF mutation and 3(3%) were with MSI. 3+ positive cases showed no BRAF mutations and were MSS tumors.

**Conclusion:** Expression of PD-L1 was found in almost twenty percent of the cases. A higher cut off was correlated with higher grade, high pathological stage and BRAF mutation. This suggests that mCRC with high PD-L1 expression may show a survival advantage with immune checkpoint inhibitors therapy. Whilst HER2 amplified mCRC is a rare occurrence, the importance of the identification of this small group of CRCs is imperative as it represents an opportunity for effective therapeutic targeting. Targeted therapy using small molecule and antibody-based therapy might show encouraging results.





# Diagnostic approach at GIS tumor

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**Introduction:** Gastrointestinal stromal tumors (GISTs) are common tumors of the gastrointestinal tract derived from the malignant precursors of the interstitial cells of Cajal. Mostly the affected patients are middle aged to elderly. GIST's are more often located in to the stomach (60–70%), while 25–35% of the GIST's are located in the small intestine. Usually, the GISTs are asymptomatic and found incidentally during endoscopic or surgical procedures.

**Results:** Male patient on 57-year consults for a routine check-up. Abdominal ultrasound revealed hypoechoogenic "tumor like" mass in the epigastrium with central liquid anechoogenic component, 50x50mm in size. The ultrasound examination couldn't clearly distinguish the origin of this lesion, so additional medical examinations were suggested. Laboratory test were without deviation. Upper gastrointestinal endoscopy confirmed submucosal formation on the greater curvature of the stomach covered with normal mucosa. On the abdominal CT was presented a submucosal tumor mass on the greater curvature without invasion of the surrounding organs. The patient was surgically treated and subtotal gastrectomy (Billroth I resection) was performed. The histopathological specimen confirmed GIST of the stomach spreading to the gastric serosa, with low mitotic rate and no metastatic deposit. The indication for target therapy (tyrosine kinase inhibitors - TKI) was suggested by an oncologist. One month after the surgery, the patient is doing well and starting the treatment with TKIs is expected.

**Conclusion:** Despite the fact that abdominal ultrasound is not primarily performed for evaluation of the gastrointestinal tract, still, in some cases it can be a first diagnostic tool for detection of gastric tumors.

**Key word:** GIST, gastric tumors, abdominal ultrasound.





# Malt Lymphoma (case report)

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**Introduction:** mucosa-associated lymphoid tissue (MALT) is extranodal lymphoid tissue scattered along mucosal linings and constitute the most extensive component of human lymphoid tissue. These surfaces protect the body from antigens. The tonsils, the Peyer patches within the small intestine and the vermiform appendix are examples for MALT. Chronic inflammation of MALT from infective or autoimmune disorders can lead to the development of extranodal marginal zone B-cell lymphomas.

**Discussion:** an ambulant scheduled gastroscopy for 69 old woman because of CT finding- thickening of the gastric wall. The patient is with no subjective complaints. She prepares for ventral hernia operation That's why CT abdomen is performed. At gastroscopy is detected irregular, vulnerable mucosal lining on the gastric body on the major curvature without spreading after air insufflation. Biopsy samples for histological analysis are taken. HP finding within General Hospital Kumanovo is gastric mucosa with relatively preserved surface epithelium, under that epithelium there are small tubular gastric glands whose epithelium shows signs of reactive atypia und severe dysplasia. In lamina propria beside mixed inflammatory infiltrate there is population of relatively monomorphic cells with eosinophilic cytoplasm and atypical oval, pleomorphic cores. Immunohistochemic analyses within Institute of pathology are necessary for immunophenotype examination of the cell population. The finding is B lymphocytic and plasmacell infiltrate (CD20+, CD 138+) and in a smaller part CD3+ and T lymphocytes. It is considerable for malignant lymphoproliferation. Because of H. Pylori test positive, eradication therapy was recommended. She was referred to Hematology clinic. PET scan shows gastric involvement and surround lymphatic nodes spreading. After six cycles of immunochemotherapy control gastroscopy with biopsy was performed and remission of the disease was found. Histological finding is surface erosive (acute exacerbated chronic) gastritis.

**Conclusion:** MALT lymphoma is indolent neoplasm of lymphatic tissue with nonspecific symptomatology. Gastrointestinal MALT lymphoma is most common. Very often is about occasional finding as it is presented case report. Because of H. Pylori infection association with development of the disease eradication of H. Pylori is important.







# Atypical presentation of gastrinoma ventriculi

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**Introduction:** On 17.06.2021, 48-years old. woman, comes for an examination at our health facility, with complaints of: weakness, loss of appetite, loss of body weight, has lost about 10 kg in the last few months, with occasional frequent bowel movements, without admixtures of mucus and blood, in visibly relatively poor general health. History of comorbidities: HTA, Non-smoker, No\_history of allergies.

**Objectives:** Multidisciplinary approach and management for early detection and treatment of the disease.

**Material and methods:** Abdominal ultrasound, Laboratory analyses, ECG, X-ray, CT of the abdomen with contrast, MRI, PET-Scan, surgical treatment.

**Results:** Abdominal echo performed at PZU "Ehomedika"-Kochani: Stomach distention was noted, with an ectopically slightly thickened wall. A suspicious vaguely circumscribed, hyperechoic formation, on a broad base, was seen in the wall. Gastroscopy and contrast-enhanced abdominal CT indicated. Lab.\_resul.: 29.06.2021: SE-15/40; Le-6.9; er-3.18; Hgb-116; TBI-26.9; trig-0.81; HDL-1.47; CKI-59; alpi-56; ldi-188; HOL-4.4; ldl-2.6; fe-15; phos-1.41; AST-22; ALT-45; CRP-0.6; Mg-1.02; urea-4.6; gluc-4.9; GGT-31; CA-2.15; creat-43; F4-14.9 pmol/L; TSH-0.208 uIU/mL; ATA<10.0; H. Pylori, serum-0.89 IU/ml, feces-negative. Gastroscopy\_13.07.2021-PHI UC for Toxicology-Skopje: End Dg: Prolapsus\_via\_cardiae. Gastritis\_chr\_cum\_intestinisatio\_susp. Pseudopolypus\_ventriculi\_pars\_proximal-is\_c.minoris-par post\_cum\_ulceratio\_superficialis. Bulbitis chr. Histological finding: Well\_differerntiated neuroendcrine tumor. PET scan 10.09.2021: Note: a well-differentiated tumor (gastrinoma) may be a low FDG avid neoplasm and the finding may be falsely negative. CT of abd. with contrast on: 28.10.2021 in PHI\_CH-Shtip: A multi-phase CT evaluation of the abdomen and pelvis was performed. The stomach was hypotonic with no visible mass. It is not well distended as it is not performed as a water dilated gastric exam. No free fluid is sent into the abdomen and small pelvis. On 04.03.2023 – Hospitalized and operated at PHI St.Naum Ohridski-Skopje, Dg. Gastrinoma ventriculi. PH finding: Intestinal metaplasia cum low gradeet high grade intraepithelial neoplasia. Angiodysplasia ventriculi.

**Conclusion:** The importance of the internist approach for early detection and treatment of neoplasms.





# Malignant neoplasm of the body of the pancreas in a patient with alcoholism and DM type-2

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**Introduction:** Pancreatic tumors can originate from the exocrine part 95% and the endocrine part of the pancreas 5%. When it comes to pancreatic cancer, it is thought of ductal adenocarcinoma.

**Objectives:** A patient at the age of 61 came in our health facility with epigastric pain, nausea, vomiting and weight loss, and they persisted a month back. Basically a patient with DM type-2 of insulin therapy for about 10 years. Etilican for about 40 years, daily alcohol consumption in larger braks.

**Materials and Methods:** The following diagnostic studies have been carried out: Laboratory analyses: Hgb 101; Er 3,55; Hct 0,292; MCV 82; Tr 210; Le 7.38; CRP 84.4; glucosa(ser) 50.24mmol/l; urea 15.7; kreatinin 167; Hba1C 8.1%; Na 119; K 4.57; Ca 2.27; Fe 6. **Serum tm markers:** CA19-9 582.5 (+); CEA 31.58 (+).

**Tm markers in ascytic liquid:** CEA 44.7 (+); CA19-9 309.9 (+); CA125 984.1 (+).

**Ultrasound abdominal find:** In a projection of the body/tail of the pancreas, hypoecho-genic and polycyclic dominantly solid focal change with dm. of almost 7cm is detected.

**Upper digestive endoscopy:** STOMACH: Mucous membrane with signs of portal gastropathy.

**Upper digestive endosonography:** With FNA obtained 2 ml of extremely dense hemorrhagic content.

**CT of abdomen with contrast:** Hepar with present focal MS changes.

**Conclusion:** Pancreatic cancer is a malignant disease with poor prognosis and a high mortality rate.

There is no screening program for early detection of pancreatic cancer, but preventive measures are being taken that may focus on modification of risk factors and lifestyle changes.

**Keywords:** malignant neoplasm of the pancreas, alcoholism DM type-2





# Diagnosis and treatment of patient with colon irritable

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**Introduction:** irritable bowel syndrome is a functional gastrointestinal disorder characterised by abdominal pain and altered bowel habit. There are three clinical forms: 1.spastic colon (chronic abdominal pain with obstipation), 2.alternately obstipation and diarrhea, and 3.chronic painless diarrhea.

**Case report:** an ambulant consultation of 48 old woman because of diarrhea and abdominal bloating. Appetite preserved, without weight loss. These complaints persist about three months. A day before actual consultation she was examined by an infectious disease specialist and infectious etiology was excluded. Altered bowel habit (alternately obstipation and diarrhea) she has had three years ago, during two months, but she was not seeking for medical help. Mental status- anxious depressive condition. Somatic status and laboratory findings (blood count, transaminases, waste products, CRP, proteins, electrolytes and lipids status) were without alterations. She was referred to the Institute of immunology for food intolerance checking. The finding was normal. Hormonal thyroid status was without alterations. Working diagnosis - Colon irritable was established. A probiotic therapy and proper diet regimen was suggested. Because of painless diarrhea a colonoscopy with biopsy was indicated to exclude microscopic colitis. A colonoscopy finding was nodulli haemorrhoidales interni gr. II. The pathological finding was normal colonic mucosa. The diagnosis Colon irritable was confirmed and a consultation with a psychiatrist was suggested. The diarrhea stops two months after she was taking antidepressants.

**Conclusion:** diagnosis of colon irritable is a matter of exclusion method. It is the most common gastrointestinal disease and it's the reason for frequent sick leaves. The treatment involves a team work by gastroenterohepatologist, psychiatrist and psychologist.





# Endoscopic surveillance of patients with chronic atrophic gastritis

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**Introduction:** atrophic gastritis is histopathologic entity characterized by chronic inflammation of the gastric mucosa with loss of the gastric glandular cells and replacement by intestinal-type epithelium, pyloric type glands and fibruos tissue. Atrophy of the gastric mucosa is the endpoint of chronic processes such as chronic gastritis associated with H. Pylori infection and autoimmunity directed against gastric glandular cells.

**Discussion:** due to period of two years (2021–2023) at our endoscopic cabinet were monitoring 12 patients (9 men, 3 women) with histologically verified atrophic gastritis on the first gastroscopy. They undergo endoscopic surveillance due to 2 years with period of 9 months between each gastroscopy. Indications for first gastroscopy were: prolonged epigastric discomfort in 4 patients and megaloblastic anemia in 8 patients. In one of the patients, 75 year old man, on the second control gastroscopy, on the pattern of atrophic gastritis, at the antral region of the gaster, there was pattern of irregular mucosa. Biopsy samples were taken. Histological finding was atrophic gastritis with severe dysplasia. In the remain 11 patients the control histological findings were the same as the previous.

**Conclusion:** chronic atrophic gastritis is a premalignant gastric condition. Adequate endoscopic surveillance of premalignant gastric conditions is prevention of gastric cancer and only way for early detection that can be potentially cured.



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## ПРВИОТ И ЕДИНСТВЕН ОРАЛЕН GLP-1 РЕЦЕПТОР АГОНИСТ ВО СВЕТОТ



Извонредно  
намалување  
на HbA<sub>1c</sub><sup>1,2,3\*</sup>



Ненадминато  
намалување  
на телесната  
тежина<sup>1,3,4</sup>



Ветувачка КВ  
безбедност со  
намалување на  
MACE<sup>5,†</sup>



\*Кај пациенти со почетна вредност на HbA<sub>1c</sub> >9%

†Во корист на орален semaglutide споредено со плацебо  
(несигнификантно)

За повеќе информации прочитајте  
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**Референци:** 1. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care*. 2019 Dec; 42(12):2272-2281. 2. Andersen A, Knop FK, Visbøll TA. Pharmacological Clinical Overview of Oral Semaglutide for the Treatment of Type 2 Diabetes. *Drugs*. 2021; 81:1003-30. 3. Rybelsus® 36ирен извештај за особините на лекот; Број и датум на решението за ставање на лекот во промет: 11-6957/2, 11-6956/2, 11-6958/2 од 11.08.2021. 4. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA*. 2019 Apr 16;321(15):1466-1480. 5. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841-851.



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