Programme and abstracts*

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Programme
10th Symposium on Portal Hypertension

	FRIDAY, JUNE 7
8.00–9.20	POSTER TOUR (SELECTED ABSTRACTS: SHORT ORAL PRESENTATION) Chair: T. Koller, M. Janicko
9.30–9.50	WELCOME ADDRESS L. Skladany, president of the Slovak Society of Hepatology J. Breza, president of the Slovak Medical Association A. Liptakova, deputy of the Ministry of Health of Slovakia
10.00–11.55	**BLOCK 1** Chair: J. Spicak, J. Lata, S. Adamcova Selcanova
10.00–10.15	BURDEN OF LIVER CIRRHOSIS IN EUROPE, AND CENTRAL EUROPE M. Janicko, Slovakia
10.17–10.37	HOW ANATOMY AND PATHOLOGY HELP TO UNDERSTAND PORTAL HYPERTENSION E. Honsova, Czech Republic
10.39–10.54	CARVEDILOL IN PORTAL HYPERTENSION R. Bruha, Czech Republic
10.56–11.11	DANIS STENT AND BALLOON TAMPONADE IN VARICEAL BLEEDING – UPDATE T. Fejfar, Czech Republic
11.13–11.28	HCV INFECTION AND LIVER CIRRHOSIS J. Sperl, Czech Republic
11.31–11.46	HBV INFECTION AND LIVER CIRRHOSIS S. Frankova, Czech Republic
11.46–11.55	**DISCUSSION**
11.55–13.00	**LUNCH**
13.00–15.00	**BLOCK 2** Chair: T. Gustot, E. Tschochatzis, I. Grgurevic
13.00–13.20	PATOPHYSIOLOGY OF PORTAL HYPERTENSION J. Gonzales Abraldes, Canada
13.22–13.42	ENDOTOXEMIA-INDUCED PORTAL HYPERTENSION: ANIMAL AND HUMAN STUDIES S.K. Sarin, India
13.44–14.04	NONINVASIVE DIAGNOSIS OF CIRRHOSIS AND PORTAL HYPERTENSION I. Grgurevic, Croatia
14.06–14.26	COAGULATION IN LIVER CIRRHOSIS V. La Mura, P.M. Mannucci, Italy
14.28–14.48	EPATOCELLULAR CARCINOMA, CIRRHOSIS AND FATTY LIVER DISEASE I. Mikolasevic, Croatia
14.48–15.00	**DISCUSSION**
15.00–15.15	**COFFEE BREAK**
15.15–16.50	**BLOCK 3** Chair: S.K. Sarin, V. La Mura, M. Papp
15.15–15.35	DOES CAIDS EXIST AND CAN IT BE DIAGNOSED IN CLINICAL PRACTICE? M. Papp, Hungary
15.37–15.57	INFECTIONS IN LIVER CIRRHOSIS E. Tsochatzis, Great Britain
15.59–16.19	STOPPING AND FUTILITY RULES IN LIVER CIRRHOSIS T. Gustot, Belgium

16.21–16.41	ACUTE VARICEAL BLEEDING – BAVENO VI AND NEWS J.G. Abraldes, Canada
16.41–16.50	**DISCUSSION**
16.50–17.05	**COFFEE BREAK**
17.05–19.00	**BLOCK 4** Chair: J.G. Abraldes, P. Jarcuska, T. Filipec-Kanižaj
17.05–17.35	NEW TREATMENTS FOR ALCOHOLIC HEPATITIS S.K. Sarin, India
17.37–18.07	ACUTE ON CHRONIC LIVER FAILURE T. Gustot, Belgium
18.09–18.29	QUALITY OF LIFE IN LIVER CIRRHOSIS T. Milovanovic-Alempijevic, Serbia
18.31–18.51	NUTRITION IN LIVER CIRRHOSIS T. Filipec-Kanizaj, Croatia
18.51–19.00	**DISCUSSION**
20.00–00.00	**DISCUSSION EVENING**
	SATURDAY, JUNE 8
8.30–10.05	**BLOCK 5** Chair: J. Sperl, I. Mikolasevic, T. Hlavaty
8.30–8.50	GUT MICROBIOME IN LIVER CIRRHOSIS L. Bajer, Czech Republic
8.52–9.12	SURGERY IN LIVER CIRRHOSIS PREOPERATIVE ASSESSMENT AND NOGO RULES M. Oliverius, Czech Republic
9.14–9.34	LIVER TRANSPLANTATION P. Trunecka, Czech Republic
9.36–9.56	PORTAL HYPERTENSION IN WOMEN Z. Zelinkova, Slovakia
9.56–10.05	**DISCUSSION**
10.05–10.15	**COFFEE BREAK**
10.15–11.50	**BLOCK 6** Chair: P. Trunecka, Z. Zelinkova, S. Frankova
10.15–10.30	AKI AND HEPATORENAL SYNDROME TYPE 1 J. Svac, Slovakia
10.32–10.47	HEPATORENAL SYNDROME TYPE 2 S. Drazilova, Slovakia
10.49–11.04	SARCOPENIA AND FRAILTY IN CIRRHOSIS T. Koller, Slovakia
11.06–11.21	EXERCISE TO TACKLE SARCOPENIA AND OBESITY IN CIRRHOSIS M. Rac, Slovakia
11.23–11.43	STATINS IN LIVER CIRRHOSIS AND PORTAL HYPERTENSION P. Jarcuska, Slovakia
11.43–11.50	**DISCUSSION**
11.50–12.00	CLOSING REMARKS L. Skladany, Slovakia
12.00–13.30	**LUNCH**
13.30	**SHS GOVERNING BOARD MEETING**

Register RH7

Ľudmila Bareková, Janka Vnenčáková, Ľubomír Skladaný

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Introduction: Register RH7 is a database of patients who were hospitalized in HEGITO, who were diagnosed with liver cirrhosis and signed informed consent for processing personal data.

Aim: To show a profile of patients hospitalised in HEGITO.

Methods: We analysed data retrospectively from register during time period from 7/2014 to 3/2019.

Results: Total number of patients was 850. 297 patients were registered during the year of 2018. 36% of patients (n = 303) died. Average age was 54 years, males comprised 59% (n = 499), females 41% (n = 351), average height was 171 cm and weight was 79 kg. Major etiology of liver cirrhosis was ALD (60%, n = 513), NASH (13.7%, n = 117), autoimmune (10.5%, n = 89), viral hepatitis (5.2%, n = 44) and others (4%). Average MELD score was 17 and Child-Pugh 9, ACLF was present in 31.5% of patients at the time of admission. Third degree ascites was diagnosed in 22% (n = 188) of patients, variceal bleeding in patients history was present in 6.4% (n = 54) of patients. Diagnosis of hepatic encephalopathy based on clinical evaluation was present in 24% (n = 202) of patients. Malnutrition based on clinical signs was present in 22% (n = 188) of patients.

Conclusion: The register offers feedback for doctors and improves quality of health care.

Incidence and consequences of bacterial infections in patients with decompensated chronic liver disease – cirrhosis

Natália Bystrianska, Svetlana Adamcová-Selčanová, Jana Vnenčáková, Tomáš Koller, Daniela Janceková, Jana Badinková, Pavol Molčan, Juraj Šváč

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Introduction: Over the last ten years, the overall mortality due to the consequences of liver cirrhosis has increased significantly and this is a continuous trend; in Slovakia it ranks 5th among all causes of mortality and Slovakia ranks 4th in Europe in this parameter. The mortality is greatly affected by infections.

Methods: Retrospective analysis of data in patients with ACLD hospitalized at HEGITO between July 2014 and September 2016.

Results: The study population included a total of 400 observed patients; inclusion criteria were satisfied by 354 patients; 95 patients (27%) had a confirmed infection complication. The occurrence of infections was as follows: urinary infections, spontaneous bacterial peritonitis and infections of respiratory tract. Approximately 49% of bacterial infections were health care associated, 35% nosocomial and 15% are community acquired. The most common type of microorganism isolated were enterococci and *K. pneumoniae*. The mortality during hospitalization was 17.9% in the population of patients with infection (p = 0.001).

Conclusion: Microbial infections represent a major problem in patients with ACLD. Early diagnosis and treatment of infection is pivotal in the management of patients with decompensated cirrhosis.

Fecal microbiota transplantation – case series. First experience in our centre

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Background: Severe alcoholic hepatitis (SAH) is one of the most serious forms of alcoholic liver disease (ALD) associated with high mortality, particularly in patients who are not suitable for corticosteroid (CS) treatment or in CS non-responders as rated by the Lille model. Unfortunately, the number of these patients is increasing and there is no alternative treatment.

Case series: From 1/2018 to 3/2019 we performed fecal microbiota transplantation in 8 patients with severe alcoholic hepatitis in our hepatology, gastroenterology and liver transplantation department (HEGITO). In this group of patients, 6 of them were non-responders to CS treatment, 1 patient was non-eligible for CS treatment

due to infection and 1 patient was a responder to CS, but the treatment had to be discontinued because of an infectious complication. In these cases we used fresh and frozen faecal material, in dosage from 40 to 100 ml, delivered via the upper GI tract during 3 to 7 days individually. The most common adverse events of FMT were diarrhoea and fever. One-month mortality after FMT was 25%.

Conclusion: Fecal microbiota transplantation appears to be safe and beneficial treatment option in patients with severe alcoholic hepatitis. However, there are still unsolved questions regarding the protocol, which should be evaluated in clinical trials.

Noninvasive liver fibrosis screening in patients with (N)AFLD and DAFLD

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Background: Estimation of the degree of fibrosis is a very important point in the management of patients with (non)alcoholic fatty liver disease (NAFLD, ALD) and dual etiology (DAFLD).

Aim: Estimation of the degree of significant fibrosis in a group of patients with NAFLD, ALD and DAFLD by noninvasive fibrosis indexes (NFI) and by transient elastography (TE).

Material and methods: In a group of 46 patients with chronic liver disease (62 ±12 years) the degree of fibrosis was determined by TE and by three NFI: Fib-4 score (Fib-4), APRI index (APRI) and NAFLD fibrosis score (NFS). The results of NFI were compared with the results of TE.

Inclusion criteria: Age over 18 years, fatty liver on ultrasound; the etiology of NAFLD, ALD, DAFLD was specified by the amount of consumed alcohol.

Exclusion criteria: Age under 18 years, any oncological diseases, autoimmune thrombocytopenia, liver cirrhosis Child Pugh B or C, a severe hematologic disease with thrombocytopenia.

Results: Significant fibrosis (F3-F4) was found in 26% of patients by TE, in 15% of patients by FIB-4 and in 17% of patients by NFS and APRI. A significant correlation was found between the age and the degree of fibrosis. From examined laboratory parameters, a significant correlation was found between the serum glycemia, AST, ALT, thrombocytes and the degree of fibrosis. Each NFI was correlated with TE. TE and Fib-4 agreed in 45.2% for cat. F0-F1, in 66.7% in cat. F2 and in 33.3% in cat. F3-F4. TE and NFS agreed in 29% for cat. F0-F1, in 33.3% in cat. F2 and in 33.3% in cat. F3-F4. TE and APRI agreed in 74.2% for cat. F0-F1, in 0% in cat. F2 and in 41.7% in cat. F3-F4. From the used NFI, the highest correlation coefficient was for FIB-4 and NFS. The highest degree of correlation with another NFI was found in FIB-4.

Conclusion: Noninvasive fibrosis indexes are appropriate for fibrosis screening in patients with NAFLD, ALD, and DAFLD, and hence the necessity of liver biopsy can be reduced. From the used NFI, FIB-4 had the highest correlation with other NFI. For the highest specificity, we recommend the use of the combination of FIB-4 with TE or combination of FIB-4 with NFS, in which the highest correlation coefficient was observed.

Precipitating factors of acute-on-chronic liver failure in hospitalized cirrhotic patients: a single-center, retrospective study

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Introduction: Patients with cirrhosis may develop acute decompensation of cirrhosis as failure of one or more organs, so-called acute-on-chronic liver failure (ACLF) syndrome, which is usually associated with a precipitating event. Recognition of the precipitating event may allow prevention of occurrence of multiorgan failure. The aim of the present study was to assess the most common precipitating factors of ACLF in hospitalized patients.

Methods: 151 consecutive cirrhotic patients who were admitted to the Department of Gastroenterology (City Hospital) between 2009 and 2011 were analyzed retrospectively. CLIF-C score was calculated for each patient according to the criteria from the EASL-CLIF Consortium.

Results: Of the 151 patients 44 fulfilled the diagnostic criteria for ACLF (29.1%; 95% CI: 22.0-37.1). Median age was 55 (IQR 43-61) years; male 57%. The underlying cause of cirrhosis was alcohol (61%). Among the patients with ACLF the in-hospital mortality rate was 16% and was higher compared to patients without ACLF

(p = 0.001). The most common of the organs exhibiting failure were liver 70.5% (95% CI: 57.0-83.9) and kidney 27.3% (95% CI: 14.1-40.5). Stratification according to the CLIF Organ Failure Score was as follows: ACLF grade 1 – 68.2% patients, ACLF grade 2 – 15.9% and ACLF grade 3 – 15.9%. The occurrence of ACLF was associated with upper gastrointestinal bleeding OR = 4.1 (95% CI: 1.5-11.2; p = 0.01). Bacterial infections were not associated with ACLF OR = 2.0 (95% CI: 1.0-4.1; p = 0.05). The white blood cell count was significantly higher in patients with ACLF 12.0 (8.4-19.2) vs. 7.1 (IQR 5.1-9.8), respectively (p = 0.001).

Conclusion: In our study the most common precipitating event for ACLF was upper gastrointestinal bleeding. Bacterial infections were not significantly associated with ACLF, but the white blood cell count was significantly higher in patients with ACLF.

Infection-associated acute tubular necrosis in critically ill patients with cirrhosis

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Introduction: Recognition of acute tubular necrosis (ATN) is very important on the background of cirrhosis as ATN predicts a poorer outcome. Patients with ATN are more likely to require renal replacement therapy than patients with HRS.

Aim: We aimed to investigate the risk factors of ATN in critically ill patients with cirrhosis.

Methods: This was a retrospective study of 142 hospitalized patients with cirrhosis (City Hospital's medical records) and of 70 outpatients with cirrhosis (Department of Forensic Medicine's autopsy database). All of them had died of cirrhosis complications between 2008 and 2010.

Results: Basic characteristics of hospitalized patients were comparable to outpatients. In total 212 patients with histologically confirmed cirrhosis were included (male 64%). Median age was 53 years (range 19-80). Mostly alcohol induced cirrhosis. ATN at autopsy among 212 patients was found in 96 patients (45.3%; 95% CI: 38.5-52.3), including hospital cases 70 (49.3%; 95% CI: 40.8-57.8) and outpatient cases 26 (37.1%; 95% CI: 25.9-49.5). Among 142 hospitalized patients ante mortem conditions were as follows: 53 met criteria of type 1 HRS (37.3%; 95% CI: 29.4-45.3) and 11 met criteria of type 2 HRS (7.8%; 95% CI: 3.9-13.4). In fact, it is interpretation of serum creatinine increase in the absence of morphological examination of kidneys. For hospitalized patients the length of stay (LOS) of the ATN group was higher than in the group without ATN: median 7 (IQR 2-12) days vs. 4 (1-10) days, respectively (p = 0.044). Out of the 212 patients, 82 patients (38.7%; 95% CI: 32.1-45.6) had various infections (pneumonia, pyelonephritis, sepsis). In our study infectious complications were associated with an 4.8-fold increase in the odds ratio of ATN (95% CI: 2.6-8.6).

Burden of liver cirrhosis in Europe and Central Europe

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Advanced chronic liver disease (aCLD), i.e. cirrhosis, histologically verified or not, creates a considerable health burden in modern society world-wide. This burden can be either health related (e.g. morbidity or mortality) or economic (cost of invalidity plus cost of health care).

Recently published data from the EASL HepaHealth project along with ongoing updates of Global Burden of Diseases show that the burden of aCLD in Europe is the largest in the world and still continues to grow. Also great differences exist among individual European countries. Median prevalence of liver cirrhosis in Europe is 833 patients per 100 000, ranging from 447 (Iceland) to 1100 (Romania). Central European countries have estimated prevalence of cirrhosis around 1000 cases per 100 000, with the exception of the Czech Republic, where the estimated prevalence is below 900 per 100 000. Mortality due to aCLD ranges from 20 to 30 deaths per 100 000 inhabitants in most central European countries, with only Hungary reaching over 30 deaths and Romania over 50 deaths per 100 000 inhabitants. In Slovakia, chronic liver disease is the 5th most common cause of death in general and the 3rd most common cause of death in the age group 40-65 years following cardiovascular diseases and neoplasms. Great concern to the society is the fact that the majority of this liver related burden affects younger, economically active people.

Because of constant health policy shifts, lack of transparency in health funding and failed DRG implementation, the economic cost of health care for patients with advanced liver disease is impossible to calculate in Slovakia.

Acute kidney injury (AKI) and hepatorenal syndrome type I (HRS I)

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Hepatorenal syndrome type I (HRS I) is the well-defined cause of prerenal AKI in patients with cirrhotic portal hypertension and ascites with high short-term mortality. The pathophysiology starts with sinusoidal portal hypertension, immediately followed by splanchnic vasodilation affecting effective arterial blood volume (EABV) and renal perfusion; inflammation and cardiac dysfunction also play a role. Currently, the standard of care in HRS I is focused on the treatment of precipitating factors and expansion of EABV with albumin and terlipressin. The latter goal is difficult to achieve because absolute amounts of body sodium and water are increased in these patients. Therefore, restoration of EABV often leads to undesirable expansion of extravascular and intravascular volume with clinically significant consequences such as pulmonary edema. In these cases, slow extracorporeal elimination techniques (i.e., CVVH w/wo dialysis) can be of benefit. Prolonged kidney hypoperfusion can lead to the development of ATN and the need for RRT with ensuing worsening of prognosis. To improve prognosis without liver transplantation, we should aim at the early detection of AKI, quick identification, and treatment of precipitants and goal-directed volume control.

Sarcopenia and frailty in cirrhosis

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Sarcopenia (SP) is considered a natural consequence of aging. It leads to a spiral of events that cause loss of muscle strength, loss of self-sufficiency, increased risk of falls and fractures, and frailty. It is often associated with a systemic inflammatory response and the risk of infection, risk of thrombotic complications and increased risk of death. A similar process occurs in patients with advanced chronic liver disease (ACLD). In those, SP appears at a younger age, but the subsequent spiral of events is identical. SP is under-diagnosed in ACLD patients mainly due to the lack of consensus on diagnostic tests. Simple tests can be useful such as the arm circumference, skin-fold thickness at the triceps or under the scapula. Another example is the global assessment of food intake and general condition using the Royal Free Hospital Prioritization Tool, which will identify patients at risk for SP. Another option is to measure the hand-grip strength, body bioimpedance or the DXA scan to quantify body components (muscle vs. fat vs. bone). The gold standard for diagnosing sarcopenia in ACLD is the measurement of total muscle area by CT scan at the level of the third lumbar vertebra divided by the square of body height. The resulting skeletal muscle index (SMI) has normal values identified in ACLD patients at < 50 cm^2/m^2 for men and < 39 cm^2/m^2 for women. SMI values have been validated among patients on the transplant waiting list predicting the outcome, but SMI has not been widely validated on other groups of ACLD patients. In addition, some studies have reported gender differences in the importance of SP in ACLD. In men, muscle mass is clearly related to the prognosis of patients. In women, many studies have not confirmed this association. It has been shown in women that subcutaneous fat is a stronger predictor of outcome compared with muscle parameters. A new trend in the United States is the measurement of frailty. It is a consequence of SP, but frailty does not mean less muscle mass, but also less muscle strength and worse body balance. A study evaluating several frailty parameters found that the hand-grip strength, the time needed for 5 chair-stands and the stability of balance at different leg positions are the best predictors of prognosis. Numerical quantification of frailty has been developed in the Liver Frailty Index (LFI), which can classify patients in three categories: frail, pre-frail and robust. LFI has been developed to predict the outcome on the transplant waiting list. However, the LFI can also be used in decompensated cirrhosis as a MELD-independent prognostic marker. In order to increase the rate of sarcopenia diagnosis, uniform and simple diagnostic tools applicable outside the centers of expertise should be agreed upon. The future of diagnosing sarcopenia will probably rely on the development of new molecular biomarkers using various new technologies.

AKI in patients with ACLD

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Introduction: Acute kidney injury (AKI) is a frequent complication in patients with ACLD. It can have prerenal, renal or postrenal etiology. A specific type of prerenal AKI in ACLD patients is hepatorenal syndrome type I (HRS I).

Aim: To determine the incidence of HRS I in ACLD patients with AKI. To identify the need for RRT and mortality in these patients.

Methods: A prospective observational study at the regular ward of the liver unit. We enrolled consecutive patients hospitalized with ACLD and recorded age, sex, etiology of ACLD, AKI, and HRS I diagnosed according to the guidelines.

Results: During three months (January 1 to March 31, 2019) we diagnosed AKI in 20 patients of average age 59 years (24-94); 12 men (60%) and eight women (40%). Fourteen (70%) had ACLD caused by ALD, 2 (10%) by NASH, 2 (10%) by viral hepatitis B and C and the rest (10%) by other etiologies. Their average MELD score was 24 (8-45), Child-Pugh score 10 (5-13). Five patients (25%) had AKI-1, 4 patients (20%) AKI-2, and 11 patients (55%) AKI-3. Five patients (25%) had AKI on CKD. The etiology of AKI in all patients was prerenal, in 9 (45%) we diagnosed HRS I. Three patients with AKI (15%) developed variceal bleeding, 9 (45%) infections: two of them were UTI, 3 RTI, and 5 SBP.

Sixteen of 20 patients (80%) were treated with human albumin, 7 of 9 with HRS I (78%) with terlipressin and albumin. Three patients with HRS (33%) needed RRT (in the form of CVVHDF) as opposed to no patient with AKI without HRS ($p = 0.037$). Resolution of AKI was observed in 10 of all patients (50%); in 5 patients (25%) it was incomplete. Five patients with HRS I died as compared to no patient with AKI without HRS I ($p = 0.0043$).

Conclusion: We diagnosed HRS I in 45% of inpatients with AKI in the context of ACLD.

Patients with HRS I had a significantly higher need for RRT and mortality as compared to patients without HRS. Of note, all the patients with need of RRT died.

Various etiology of advanced chronic liver disease as a cause of sarcopenia

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Introduction: Malnutrition is a common complication of chronic liver disease regardless of the etiology of these diseases. In ACLD patients, it is represented by loss of muscle mass (sarcopenia). CT measurement of muscle mass is the gold standard for diagnosis of sarcopenia. Liver frailty index (LFI) is the method of measuring muscle mass performance. The amount and performance of muscles is crucial for prognosis of patients with ACLD, especially after liver transplantation. A nutritional intervention consisting of nutritional supplementation and exercise may be helpful in achieving a better prognosis in these patients.

Aims: The primary goal was to find out if the different etiology of ACLD could contribute to a higher risk of sarcopenia in these patients. The secondary goal was to look for a useful method to evaluate sarcopenia. The amount of muscle mass was measured by anthropometric parameters and CT analysis. Muscle mass performance was evaluated using the liver frailty index (LFI).

Methods: In the follow-up were included patients admitted to HEGITO with decompensated advanced chronic liver disease (d-ACLD) who were considered for liver transplantation (LTx). Each patient with decompensated ACLD was considered malnourished and nutritional intervention was initiated. We monitored demographic and anthropometric parameters, and etiology of ACLD. Psoas muscle area measured by CT was used for evaluation of the amount of muscle mass. We used the liver frailty index to measure muscle performance.

Results: Alcohol liver disease was the first cause of ACLD, followed by non-alcoholic steatohepatitis. We found that different aetiology of ACLD does not affect the risk of sarcopenia. CT determination of muscle mass with PMA at level L3 is a reliable diagnostic tool for sarcopenia. The liver frailty index appears to be an easy bedside method of evaluating muscle performance in ACLD patients.

Conclusion: Malnutrition is represented by sarcopenia in patients with ACLD. This is a common complication of ACLD. EASL guidelines consider CT examination of muscle mass as the gold standard for the diagnosis of sarcopenia. Muscle mass performance appears to be crucial for determining the prognosis of ACLD patients. ACLD LFI measurement is a promising method reflecting the prognosis of an ACLD patient.

Age-dependent peculiarities of cardiovascular alterations in nonviral liver cirrhosis patients

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Introduction: Some of the most frequent and prognostically unfavorable complications in liver cirrhosis (LC) patients are alterations of the cardiovascular system, which include damage of the myocardium, injury of major vessels and disorders of the microcirculation. Violations of systemic hemodynamics correlate with the activity of the fibrotic process in the liver, changes in portal blood flow parameters and are inherent for most LC patients. The aim of the study was to investigate age-dependent cardiovascular alterations in patients with nonviral liver cirrhosis.

Material and methods: Echocardiography and investigation of atrial natriuretic propeptide (proANP) were carried out in 57 LC patients. All of them were divided according to their age into three groups: the 1st group included 17 patients aged 30 to 44 years, the 2nd group – 24 patients with age 45-59 years, the 3rd group – 16 patients aged 60 to 74 years. Three control groups, each consisting of 10 healthy individuals representative by age and gender to the study groups, were involved in the study. Echocardiography was performed using the ultrasound diagnostic system En Visor HDS (Philips Ultrasound System, USA). ProANP plasma level was measured by ELISA analyzer Statfax 303+ (USA) using the set of reagents "Biomedica" (Austria). Informed consent was obtained from all the participants.

Results: It was established that mature and elderly patients had increased sizes of the left atrium and right ventricle, end systolic left ventricle size, left ventricle posterior wall thickness in the diastole, interventricular septum thickness in systole and diastole, left ventricular myocardial mass, left ventricular myocardial mass index and relative thickness of its walls. Ejection fraction was decreased in mature and elderly patients at 8.1% and 7.3%.

Exercise to tackle sarcopenia and obesity in cirrhosis

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Sarcopenia is defined as the generalized loss of muscle mass, muscle strength, and muscle function. Malnutrition, sarcopenia and physical deconditioning are frequent complications in patients with liver cirrhosis. Physical inactivity, sarcopenia, and frailty are highly prevalent, independent predictors of morbidity and mortality in patients with cirrhosis. The progression of malnutrition correlates with liver failure.

Impaired dietary intake, chronic inflammation, altered macro- and micronutrient metabolism, and low physical activity are the most common causes. In the case of cirrhosis muscle tissue can be depleted. Sarcopenia is one of the most common complications of cirrhosis, leading to frailty. Frailty is the end result of prolonged sarcopenia and physical deconditioning. Sarcopenia is an independent predictor of lower survival in cirrhosis and in patients undergoing liver transplantation. Sarcopenia may occur in obese patients with cirrhosis. Malnutrition, obesity and sarcopenic obesity may worsen the prognosis of patients with liver cirrhosis and lower their survival also in NASH cirrhosis. Exercise improves skeletal muscle mass, strength, endurance, and cardiopulmonary function. Some of its proven benefits (insulin sensitivity) are of particular interest to ESLD patients with a multisystemic disease such as NASH. Exercise can improve body composition including weight, body mass index (BMI), visceral and subcutaneous fat mass, HOMA-IR and aminotransferase levels. Exercise in these patients can decrease interleukin 6 (IL-6) and leptin, and also improve adiponectin. Reversal of sarcopenia is challenging. Prevention during early stages of liver disease should be the main goal. Dietary and moderate exercise interventions are consistently beneficial and safe. The evidence for the benefit of exercise in cirrhosis is promising. Moderate intensity exercise is safe for ESLD patients. Clinical trials have shown that exercise improves sarcopenia and portal hypertension. However, evidence for the benefits of exercise for clinical outcomes derived from large clinical trials is still missing. For patients with ESLD it is recommended to perform 30-60-minute exercise sessions combining both aerobic and resistance training, in summary to achieve 150 minutes/week, with a parallel removal of inactivity. Large long-term studies are needed to test improved survival.

Assessment of adiponectin and clinical and metabolic risk factors in patients with NAFLD and metabolic syndrome

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Introduction: Nonalcoholic fatty liver disease (NAFLD) represents the most common cause of chronic liver disease. It is regarded as a spectrum of hepatic conditions, which ranges from simple liver steatosis through nonalcoholic steatohepatitis (NASH), with or without fibrosis, to cirrhosis as end stage liver disease. It has been associated with the development of metabolic syndrome (MS), which is an interrelated cluster of risk factors for cardiovascular disease and type 2 diabetes such as hyperglycemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels and central obesity. NAFLD and MS are strongly connected civilization disorders with continuous growing worldwide incidence rates. This clinical condition is closely associated with visceral obesity and other features of the MS including insulin resistance, dyslipidemia and increased cardiovascular risk. Therefore, NAFLD is considered as a hepatic manifestation of MS. The growing rates of this obesity-related syndrome have spurred the search for greater insight about mechanisms contributing to the development of MS, especially those reflecting a dysfunction of adipose tissue, which probably plays a major role in its development.

Numerous studies have demonstrated that adipokines, secreted from adipose tissue, are involved in various processes, such as inflammation, immunity, insulin sensitivity, simple liver steatosis and NASH. Adiponectin is an adipokine, which is associated with an anti-inflammatory effect and by suppressing the release of pro-inflammatory cytokines. Thus, adiponectin deficiency is related to a pro-inflammatory condition. Adiponectin is a major regulator of glucose and lipid homeostasis by its insulin sensitizer properties. Since decreased insulin sensitivity is linked to MS, decreased adiponectin levels may be related to its development.

The purpose of this study was to investigate the relationship between adiponectin levels and MS components in patients with MS and without MS, and assess the association between risk factors of both disorders as well. Our study also tried to assess the association between risk factors of mentioned conditions to amend diagnostic approaches by using groups of tests and simple scoring systems for assessment of steatosis and fibrosis, which are composed of routine clinical and laboratory parameters.

Material and methods: Our study group consisted of 143 subjects, who included 80 patients with NAFLD and 63 healthy subjects. In the patient group, a wide spectrum of hepatic conditions was present, with or without fibrosis. All subjects were classified according to the presence of MS and they were divided into subgroups with and without MS. Steatotic and fibrotic indices (fatty liver index [FLI], APRI test, NAFLD fibrosis score, and FIB-4 test) were calculated in the patient group and subgroups with and without MS and defined their statistical significance and correlations. The insulin resistance index was determined according to the homeostatic model assessment of insulin resistance (HOMA-IR). Each subject underwent a wide spectrum of laboratory and clinical investigations. Ultrasound investigation and transient elastography were performed in the patient group. In patients and control subjects blood samples were drawn after an overnight fast for analysis of total levels of adiponectin (measured using the enzyme-linked immunosorbent assay), lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), fasting glucose, glycated haemoglobin (HbA_{1c}), insulin, apoprotein-A1, apoprotein-B, CRP, interleukin (IL-6), interleukin (IL-10), iron, ferritin, haptoglobin, alpha-2 macroglobulin, uric acid, creatinine, urea, liver tests (bilirubin, ALT, AST, AST, ALP, GMT, cholinesterase, total proteins, albumin), haematological parameters and coagulation parameters including fibrinogen. Prevalence and statistical significance of risk factors, such as abdominal obesity, hyperglycemia, atherogenic dyslipidemia and elevated blood pressure were determined.

Results: Our study proved increased prevalence of MS in NAFLD patients. We found that in the group of patients with simple liver steatosis hyperglycemia, obesity and elevated serum triglycerides were the most risky MS components, while in patients with NASH they were hyperglycemia and low HDL cholesterol level. The most frequent risk factor was abdominal obesity. FLI was a sensitive steatosis index and APRI and NAFLD fibrosis score and the FIB-4 test were reliable fibrosis indices even in patients with MS. The cut-off point of 70 for FLI demonstrated 84% sensitivity for liver steatosis.

The mean values of adiponectin in all patients were lower (4.28 ± 2.62 μg/ml) compared with the control group (11.69 ± 3.99 μg/ml). In the subgroup of patients with MS the mean values of adiponectin (3.28 ±1.88 μg/ml) were statistically significantly different to the subgroup without MS (5.42 ± 3.36 μg/ml, $p \leq 0.02$).

The mean adiponectin levels were significantly lower in the presence of lower HDL cholesterol. In the patient group mean values of HDL cholesterol (1.28 ± 0.28 mmol/l) were

significantly different compared to the control group (1.62 ± 0.26 mmol/l) ($p \leq 0.0002$) and also when comparing the control group with the subgroup of patients with MS (1.46 ± 0.26 mmol/l), $p \leq 0.02$). There were present positive correlations of adiponectin with HDL cholesterol in subgroups with MS ($r = 0.28$, $p \leq 0.02$) and also in subgroups without MS ($r = 0.44$, $p \leq 0.0002$).

The mean values of triglycerides in all patients were significantly higher (1.93 ± 0.83 mmol/l) compared to the control group (1.38 ± 0.41 mmol/l) ($p \leq 0.03$) and also mean values of triglycerides in the subgroup with MS (2.15 ± 1.01 mmol/l) compared to the control group ($p \leq 0.05$). There was a significant negative correlation between adiponectin and triglycerides in subgroups without MS ($r = –0.326$, $p \leq 0.01$).

The mean values of glucose in the patient group were significantly higher (6.30 ± 2.13 mmol/l) compared to the control group (5.17 ± 0.50 mmol/l) ($p \leq 0.04$) and also in the subgroup of patients with MS (6.72 ± 2.42 mmol/l) compared to the control group. There were significant negative correlations between the adiponectin subgroup with MS and the glucose subgroup with MS ($r = –0.43$, $p \leq 0.0003$) and also between subgroups without MS ($r = –0.39$, $p \leq 0.001$).

The mean values of HOMA-IR in the patient group (6.88 ± 4.87) were significantly higher compared to the control group (3.13 ± 1.29) ($p \leq 0.004$) and also comparing subgroups of patients with MS (8.59 ± 6.03) to the control group ($p \leq 0.02$). Also between the subgroup of patients without MS (4.66 ± 2.90) and the control group there was a significant difference ($p \leq 0.02$). There was significant negative correlation between adiponectin in the subgroup of patients without MS and HOMA-IR ($r = –0.454$, $p \leq 0.0001$).

We also confirmed a significant negative correlation between adiponectin and BMI in the patient group ($r = –0.275$, $p \leq 0.03$), between the adiponectin subgroup with MS and the BMI subgroup with MS ($r = –0.409$, $p \leq 0.001$) and also between the adiponectin subgroup without MS and the BMI subgroup without MS ($r = –0.24$, $p \leq 0.05$).

Discussion and conclusion: The pathogenesis of NAFLD has not been fully understood. It is generally accepted that NAFLD is pathogenically a multiple-hit disease. According to this hypothesis, NAFLD is a complex disease mediated by several metabolic, environmental, genetic and microbiological mechanisms [1].

The main role in the development of NAFLD is played by an elevated level of circulating free fatty acids in conjunction with insulin resistance causing excessive accumulation of triglycerides in hepatocytes [2, 3]. Additionally it is responsible for lipotoxicity, oxidative stress and the inflammatory response, predisposing to progressive liver damage [4]. Recent studies have revealed that multiple mechanisms, acting synergistically in genetically predisposed individuals, are involved in the development and progression of NAFLD [4, 5].

We conclude that the diagnostic and prognostic approach in NAFLD and MS should be completed with algorithms of clinical, biochemical, and imaging methods and indices for steatosis and fibrosis (FLI, NAFLD fibrosis score, APRI test, FIB-4 test), which are easily applicable in routine clinical practice. It is diagnostically and prognostically important to determine also indices of insulin sensitivity or insulin resistance (HOMA-IR) in patients with NAFLD and MS. We demonstrated that lower circulating total adiponectin levels were associated with the presence of the criteria of MS. This association was independent of age and sex, smoking status, and waist circumference. Longitudinal data of prospective population-based studies might be used to understand the role of adiponectin in the development of MS. Early and proactive diagnosis of MS and its severity will allow medication and lifestyle optimization, in order to prevent the occurrence of organ complications and improve health-related quality of life.

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References

1. Belhayara MI, Mellouk Z, Hamdaoui MS, et al. Relationship between the insulin resistance and circulating predictive biochemical markers in metabolic syndrome among young adults in western Algeria. Diabetes Metab Syndr 2019; 13: 504-509. doi: 10.1016/j.dsx.2018.11.019.
2. Yanai H, Yoshida H. Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. Int J Mol Sci 2019; 20: 1190; https://doi.org/10.3390/ijms20051190.
3. Sasso FC, Pafundi PC, Marfella R, et al. Adiponectin and insulin resistance are related to restenosis and overall new PCI in subjects with normal glucose tolerance: the prospective AIRE Study. Cardiovasc Diabetol 2019; 18: 24. doi: 10.1186/s12933-019-0826-0.
4. Satish M, Saxena SK, Agrawal DK. Adipokine dysregulation and insulin resistance with atherosclerotic vascular disease: metabolic syndrome or independent sequelae? J Cardiovasc Transl Res 2019. doi: 10.1007/s12265-019-09879-0.
5. Stroescu RF, Mărginean O, Bizerea T, et al. Adiponectin, leptin and high sensitivity C-reactive protein values in obese children – important markers for metabolic syndrome? J Pediatr Endocrinol Metab 2019; 32: 27-31. doi: 10.1515/jpem-2018-0378.

Danis stent and balloon tamponade in variceal bleeding – update

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Acute variceal bleeding as ascites and hepatic encephalopathy are the most severe complications of portal hypertension, which is mainly caused by liver cirrhosis.

In the general population of patients with liver cirrhosis, the annual risk of variceal bleeding is approximately 4%; however, in patients already diagnosed with major varices (F2-F3) this exceeds 10-15%. Varicose bleeding is therefore the most life-threatening complication of portal hypertension, and at the same time the third leading cause of bleeding in the upper gastrointestinal tract. Even with intensive therapy, the first episode of bleeding has high mortality (10-15%); two-thirds of patients who die due to bleeding do so in the first 24 hours. Especially in the first five days, the attack is associated with a high risk of bleeding recurrence (40% relapse).

Treatment always requires an intensive multidisciplinary approach to the patient with the participation of the endoscopic team and intensivists. Basic treatment consists of a combination of vasoactive drugs, volume expansion, appropriate hemosubstitution, broad spectrum antibiotics and endoscopic treatment. In the case of treatment failure, TIPS can be indicated or to bridge the critical period one can use a balloon tamponade or dedicated esophageal stent.

Balloon tamponade has a life-saving effect, but is associated with a number of complications and insufflated can be used up to 12-24 hours only.

Urgent transjugular intrahepatic portosystemic shunt (TIPS) is indicated in cases of failure of first-line methods. As a salvage therapy, it is currently difficult to find an alternative. Studies with a larger number of patients achieved immediate control of bleeding in the range 91-100% of cases. Even TIPS has its contraindications and limitations dependent on the progress of the liver disease, and TIPS availability.

Danis stent

Self-expandable metallic stents (SEMS) have, for a long time, been used in the treatment of malignant oesophageal stenosis, leaks and perforations of the oesophagus or tracheo-oesophageal fistula. The idea of using the force of the self-expandable stent to compress the bleeding oesophageal varices and stop the bleeding originated at the turn of the millennium. Its father was a Slovak, born in Lučenec – Associate Professor Jan Danis MD – who placed the stent for the first time in this indication, in 2002. After a period of development and testing the stent in animal models, the first stents dedicated to this therapy were used in clinical trials in 2003 and today take the name Danis. In 2010 Baveno V included this method in the recommendation, as a possible alternative for treatment of refractory variceal bleeding from oesophageal varices. Since 2010 other prospective data with more than 140 patients have been published, providing a high success rate in terms of bleeding and low risk of complications. In 2013 the first RCT comparing balloon tamponade and stent, showing a significantly higher bleeding control rate and lower complications, favoured the Danis stent.

Moreover, in patients with progressive liver disease at high risk of recurrence, it allows even longer restitution of liver function after the haemorrhage and, in some cases, allows subsequent treatment with TIPS. The big advantage above all is the relatively easy stent placement. At the last Baveno consensus meeting conference it was confirmed that a metal stent may be as efficacious and a safer option than BT in refractory esophageal variceal bleeding (evidence 3, B). Also, over the last years some data have been published on the use of the Danis stent outside of variceal bleeding too (laceration of oesophagus, anastomotic leak).

References

1. De Franchis R (ed.). Portal Hypertension V: Proceedings of the Fifth Baveno International Consensus Workshop. 5th ed. Wiley-Blackwell Press, London 2011.
2. De Franchis R. Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743-752.
3. Hubmann R, Bodlaj G, Czompo M, et al. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. Endoscopy 2006; 38: 896-901.
4. Zehetner J, Shamiyeh A, Wayand W, Hubman R. Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. Surg Endosc 2008; 22: 149-52.
5. Wright G, Lewis H, Hogan B, et al. A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. Gastrointest Endosc 2010; 71: 71-78.
6. Dechen A, El Fouly AH, Bechmann LP, et al. Acute management of refractory variceal bleeding in liver cirrhosis by self-expanding metal stent. Digestion 2012; 85: 185-191.
7. Escorsell À, Pavel O, Cárdenas A, et al. Variceal Bleeding Study Group. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology 2016; 63: 1957-1967.
8. T. Fejfar, T. Vaňásek, R. Brůha, et al. Léčba krvácení v důsledku portální hypertenze při jaterní cirhóze – aktualizace doporučených postupů ČHS ČLS JEP. Gastroent Hepatol 2017; 71: 105-116.
9. Mishin I, Ghidirim G, Dolghii A, et al. Implantation of self-expanding metal stent in the treatment of severe bleeding from esophageal ulcer after endoscopic band ligation. Dis Esophagus 2010; 23: E35-8.

Non-invasive assessment of hepatic venous pressure gradient in liver transplant candidates

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Introduction: Subjects with liver cirrhosis and clinically significant portal hypertension have the hepatic venous pressure gradient (HVPG) >10 mm Hg. Cirrhotic patients with the HVPG > 12 mm Hg have high risk of variceal bleeding and those with HVPG > 16 mm Hg. HVPG has a significant predictive value in cirrhotic patients and may help in the selection of the appropriate treatment modality. Direct measurement of HVPG by hepatic vein catheterisation is an easy but invasive procedure. Non-invasive assessment of HVPG based on liver stiffness measurement or assessment of plasma markers of liver fibrosis and portal hypertension has not been reliable enough especially if HVPG exceeded 10 mm Hg. We presumed that liver transplant candidates might represent a suitable study group owing to the absence of active drinkers. The aim of the study was to demonstrate that in clinically stable cirrhotic patients, a correlation between HVPG and non-invasive markers may be found also for values of HVPG higher than 10 mm Hg.

Material and methods: The study group included 119 patients with liver cirrhosis (81 males and 38 females, mean age 58.2 ± 11.5 years). One hundred and seven of 119 patients were liver transplant candidates. Aetiology of cirrhosis was: alcoholic 44, viral 23, cholestatic 20, non-alcoholic steatohepatitis 11, autoimmune 11, cryptogenic 11 and Wilson's disease 2. Twelve of 119 patients were patients with compensated liver cirrhosis after chronic hepatitis C virus treatment with direct-acting antivirals. The patients underwent direct HVPG measurement by hepatic vein catheterisation, liver stiffness measurement by 2-dimensional shear-wave elastography (Aixplorer Multiwave, manufacturer Supersonic Imagine, France) and a blood sample drawn for non-invasive plasma markers assessment (osteopontin, VCAM-1, IL-6, TNF-α, IL-1ra/IL-1F3 and ELF score).

Results: Values of liver stiffness ranged from 9 to 62 kPa and values of HVPG ranged from 6 to 32 mm Hg. The correlation between HVPG and liver stiffness was linear (R = 0.674, $p = 2 \times 10^{-7}$) and maintained linearity also for values of HVPG higher than 10, resp. 16 mm Hg. Plasma osteopontin and VCAM-1 concentrations showed a linear correlation with HVPG (R = 0.415, $p = 4.03 \times 10^{-6}$; R = 0.383, $p = 2.47^{-5}$, respectively). Areas under the ROC curve for the cut-off value of HVPG 16 mm Hg were 0.83 for liver stiffness (sensitivity 80%, specificity 75%), 0.70 for serum osteopontin (sensitivity 80%, specificity 55%) and 0.71 for serum VCAM-1 (sensitivity 80%, specificity 45%). The remaining plasma markers showed a weak correlation with HVPG and were evaluated as not suitable for clinical use.

Conclusion: We confirmed our hypothesis that in clinically stable cirrhotic patients, the correlation between HVPG and liver stiffness or plasma markers of portal hypertension is close and linear also for high values of HVPG. Liver stiffness was found to be the most accurate non-invasive predictor of HVPG. Among plasma markers only concentrations of osteopontin and VCAM-1 seemed to be reliable enough for further clinical evaluation.

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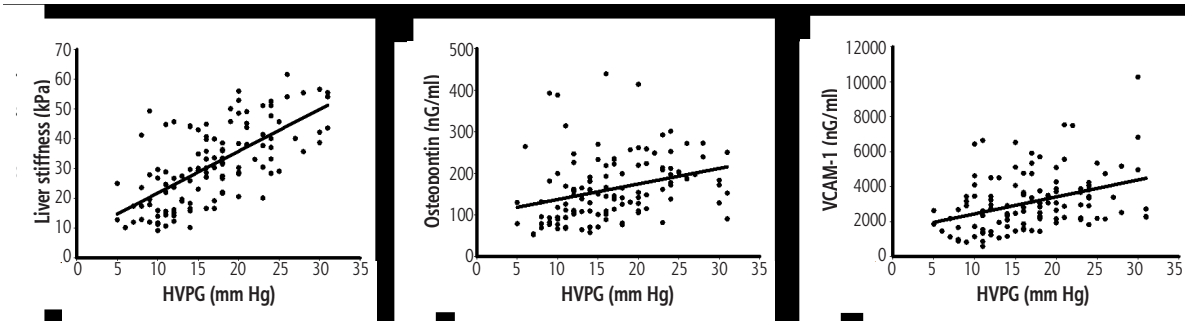

HBV infection and liver cirrhosis

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As a consequence of vaccination and other preventive measures, the epidemiology of HBV infection has stabilized in Western countries. The development of effective antiviral therapies over the years has led to improved survival in HBV patients and reduced HCC incidence.

The estimated 5-year progression rate from chronic hepatitis to cirrhosis is between 12% and 20%. The annual rate of progression from chronic hepatitis to cirrhosis has been estimated to be 2% to 5% for HBeAg-positive and 3% to 10% for HBeAg-negative patients. The higher rate in HBeAg-negative is related to older age and more advanced liver disease at presentation. Factors that have been reported to be associated with an increased rate of progression to cirrhosis include: host (older age, male, obesity), virus (persistent high levels of HBV replication, HBV genotype C > B), coinfection with other viruses (HCV, HDV, HIV) and environmental factors (alcohol). The estimated 5-year progression rate from compensated to decompensated cirrhosis is 20% to 23%, and the annual rate of progression from compensated cirrhosis to hepatic decompensation has been estimated to be 3% to 5%. Among untreated patients, survival after the development of compensated cirrhosis is favourable initially (85% at 5 years) but decreases dramatically after the onset of decompensation to between 55% and 70% at 1 year and 14% to 35% at 5 years. Rates of progression and survival have markedly improved in the era of nucleos/tide analogues, even among patients who have decompensated cirrhosis.

The annual rate of HCC development has been estimated to be 0.5% to 1% for noncirrhotic patients and between 2% and 3% for patients with cirrhosis. It is important to note that although HCC is more common among patients with cirrhosis, 30% to 50% of HCC associated with HBV occurs in the absence of cirrhosis. HBV carriers have more than a 100-fold increase in the risk of HCC. Host, viral and environmental factors play a role in HCC development. In addition to factors associated with cirrhosis development, race, diabetes, obesity, core promoter variants, smoking and aflatoxin exposure have been reported to be associated with HCC development. Several prediction models have been developed to assess the risk for HCC. These models were derived from data in Asian patients, most of whom acquired HBV infection perinatally and were infected with HBV genotype B or C.

It is essential to know the precise HBV status of the patient and in particular the existence of HBV replication. Whatever the level of HBV DNA, if detectable, antiviral treatment with entecavir or tenofovir should be started as soon as possible in patients with cirrhosis. The antiviral treatment has two objectives: 1) the improvement of liver function; and 2) to decrease the risk of HBV recurrence after liver transplantation (LT) in patients with decompensated liver disease or HCC indicated for LT.

Since interferon treatment is contraindicated in advanced cirrhosis, the only choice for these patients is treatment with NUCs. Lamivudine first and adefovir have been widely used to treat HBV in cirrhotic patients. However, tenofovir and entecavir are currently the first-line drugs with a greater antiviral potency and higher barrier to resistance. In case of previous resistance to lamivudine, tenofovir is the drug of choice, showing a good safety profile even in patients with advanced liver disease. Lactic acidosis has been reported in some patients with a MELD score > 20, particularly when treated with entecavir. About one third of patients with decompensated cirrhosis who initiate therapy have improvement in liver function.

HCV infection and liver cirrhosis

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HCV infection is acquired via blood contact. HCV RNA is detected in blood 7-21 hours after infection. The quantity of HCV RNA increases substantially and is followed by liver aminotransferases elevation 4-12 weeks after infection. Only a minority of patients present with clinical symptoms of liver disease; most remain asymptomatic in the acute phase and are not aware of the disease. The studies on natural history of HCV show that 55-86% of infected individuals are not able to eliminate the virus spontaneously and the disease progresses to a chronic course. Women and younger individuals achieve spontaneous clearance of the virus more often. Spontaneous clearance is also more frequent in *IL28B* rs12979860 CC carriers. When chronic, spontaneous clearance of the infection is extremely rare. Even if the liver disease caused by HCV has a mild activity and a slow course in most cases, epidemiological studies prove a considerable mortal-

ity associated with HCV infection. Liver cirrhosis develops in 15-30% of infected individuals within 10-20 years; the time to develop HCC is approximately 20-30 years. Prospective studies in immunocompromised hosts, i.e. HIV co-infected patients or those with hypogammaglobulinaemia, show an increased risk of cirrhosis development in HCV infection. Contrarily, immunocompetent subjects show a mild course of the disease in the first 20 years of chronic infection. The highest incidence of cirrhosis is described after 25 years of disease duration, but the overall survival was not influenced by HCV; 35% of infected individuals developed cirrhosis but nobody with normal values of liver function tests over a long period.

The relatively mild course of the disease is in sharp contrast with the number of liver transplants owing to HCV infection and the overall HCV-associated mortality. The course of the disease is thus influenced by many risk factors present in otherwise healthy individuals. The following factors unfavourably influence the course of the liver disease. The age is crucial. Older age at the time of liver biopsy and the duration of the illness are associated with a higher degree of liver fibrosis. An accelerated course is also associated with significant alcohol consumption (> 50 g daily), diabetes, obesity, HIV and HBV co-infection and non-alcoholic steatohepatitis. Patients infected with genotype 3 of the virus also present with faster fibrosis progression and have an increased risk of HCC.

The burden of chronic hepatitis C changed after introduction of direct-acting antivirals in clinical practice in 2013. Currently available treatment regimens consisting of two or three direct-acting antivirals drugs are able to cure more than 90% of compensated and decompensated cirrhotic patients regardless of HCV genotype. Direct-acting antiviral treatment regimens are well tolerated and safe also in cirrhotic patients. Achievement of a sustained virologic response in cirrhotic patients is associated with a significant decline in risk of decompensation and liver-related death. Approximately one third of decompensated cirrhotic patients could be removed from the waiting list to liver transplantation owing to the improvement of liver function. A significant decline in the number of liver transplants due to HCV has been documented in the United States since 2014. Unfortunately, the majority of individuals infected with hepatitis C virus remain undiagnosed and their liver disease slowly progresses towards liver cirrhosis. A modeling study predicted a decline in hepatitis C related deaths after 2030. Conditions for such a positive course are population screening and screening programs in high-risk populations, and the immediate treatment of infected individuals with direct-acting antivirals.

References

1. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009; 461: 798-801.
2. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis 2013; 57: 230-236.
3. Seeff LB, Miller RN, Rabkin CS, et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. Ann Intern Med 2000; 132: 105-111.
4. Kim WR, lake JR, Smith JM, et al. OPTN/SRTR 2017 Annual Data Report: Liver. Am J Transplant 2019; 19 (S2): 184-283.
5. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018; 69: 461-511.
6. European Union HCV Collaborators. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. Lancet Gastroenterol Hepatol 2017; 2: 325-336.

Liver transplantation – current challenges

Pavel Trunečka

IKEM

For more than 5 decades liver transplantation (LTx) has been a well-established therapeutic intervention. Currently, almost 8 000 LTx are performed in Europe annually, out of which only 3% are from live donors [1]. In some institutions graft and patient survival surpasses 79% and 84% at 10 years, and 49% and 53% at 20 years from the procedure.

In many European countries, donor shortage is the limiting factor for many candidates to get a transplant; but neither the number of LDLT nor the splitting of the liver increased substantially. Instead development is focused on progress in machine preservation (either hypothermic or normothermic oxygenated perfusion). These methods aim to increase the donor pool by using marginal donors, especially donors after cardiac deaths, and possibly test or even improve metabolic activity of the graft during the storage [2].

The progress in transplantation surgery in the last years was focused more on increasing the safety of the procedure, and to a lesser extent on surgical innovations (more intensive use of auxiliary liver transplantation for acute liver failure, dual donor liver transplantation, innovative technique for portal vein thrombosis, and venous outflow modification). In countries performing LDLT laparoscopic hepatectomy became standard.

There is ongoing improvement in intensive care for liver transplant candidates and recipients, especially those with acute-on-chronic liver failure [3], patients with severe renal impairment before liver transplantation, care for patients with acute liver failure, and for infectious complications after the procedure. Preparation and postoperative care for AB0 incompatible recipients became readily available for patients in need.

Indications for liver transplantation was until recently well established, but the field is now under review due to new approaches aiming to offer a survival benefit also for patients who were until now doomed to death under the best conservative therapy currently available. These are the patients with acute-on-chronic liver failure, particularly patients with acute alcoholic hepatitis with a high Lille score that could be accepted by several programs worldwide [4]. Hopefully guidelines from the consensus conference held in April 2019 in Dallas will be available timely. The increasing number of patients with HCC, especially patients with sizable tumors beyond the Milan criteria, raises the need for pre-transplantation care aiming to downstage the tumors while limiting access to transplantation for candidates with high probability of tumor recurrence [5]. The transplant waiting list is now opened also for patients with small hilar cholangiocellular carcinoma (CCA) in centers that embarked on the Mayo protocol for CCA [6]. Research interest in treating patients with nonresectable metastases of colorectal carcinoma [7] was materialized in ongoing trials in Scandinavia and France, which could bring results as early as in 2023. NAFLD/NASH and its world epidemics still did not change the situation in the Czech republic, but in some countries NASH cirrhosis became the leading indication for LTx. This change could bring a high burden to hospital service, both pre-transplant and post-transplant, due to numerous comorbidities in these patients.

With increasing numbers of patients surviving LTx, many of them several decades, the extent of follow-up services is becoming exhausting for transplant professionals. Positive changes could be achieved in patients transplanted for HCV related cirrhosis, as these can be treated post-transplant conveniently with DAA with excellent results. Other recurrent diseases requiring continuous attention are PSC and autoimmune hepatitis, especially in young recipients. NASH is present in up to 10 percent of patients in biopsies at 5 years after transplantation [8] but does not affect the overall survival.

Maintenance immunosuppression did not change much during the last decade. The M-tor inhibitor sirolimus failed the Silver study aiming to prolong recurrence-free survival of recipients transplanted for HCC. Everolimus failed the "Tacrolimus elimination study" due to its low immunosuppressive activity in the tacrolimus elimination arm [9]. The belatacept trial on de-novo liver transplant recipients was stopped due to excess mortality in all three belatacept arms [10]. Thus only tacrolimus, mostly its once-daily modifications, is currently the mainstay of immunosuppression for liver graft recipients. The "Commit" recommendation aims at limiting modifiable risk factors for graft and patient survival by improvement in long-term therapy [11].

The last decade changed the view of liver allograft rejection, turning attention to humoral immunity that leads to more laboratory testing of HLA antibody especially in cases of unidentified allograft dysfunction. Diagnostic criteria for antibody mediated rejection recently established at the last Banff meeting [12] highlighted the need for protocol biopsies and the role of preformed and *de novo* donor specific HLA antibodies.

After more than five decades of development in the field of liver transplantation, there is still space for improvement despite dramatic changes that could hardly be expected.

References

1. Newsletter transplant 2018 Council of Europe. http://www.transplant-observatory.org/download/6732/
2. Weissenbacher A, Vrakas G, Nasralla D, Ceresa CDL. The future of organ perfusion and re-conditioning. Transpl Int 2019. doi: 10.1111/tri.13441.
3. Gustot T, Agarwal B. Selected patients with acute-on-chronic liver failure grade 3 are not too sick to be considered for liver transplantation. J Hepatol 2017; 67: 667-668.
4. Gelu-Simeon M, Mathurin P. Liver transplantation for severe alcoholic hepatitis: where are we now? Liver Transpl 2018; 24: 1327-1328.
5. Cillo U, Vitale A, Polacco M, Fasolo E. Liver transplantation for hepatocellular carcinoma through the lens of transplant benefit. Hepatology 2017; 65: 1741-1748.
6. Goldaracena N, Gorgen A, Sapisochin G. Current status of liver transplantation for cholangiocarcinoma. Liver Transpl 2018; 24: 294-303.
7. Gorgen A, Muaddi H, Zhang W, et al. The new era of transplant oncology: liver transplantation for nonresectable colorectal cancer liver metastases. Can J Gastroenterol Hepatol 2018; 2018: 9531925. doi: 10.1155/2018/9531925.
8. Hejlova I, Honsova E, Sticova E, et al. Prevalence and risk factors of steatosis after liver transplantation and patient outcomes. Liver Transpl 2016; 22: 644-655.
9. Geissler EK, Schnitzbauer AA, Zülke C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. Transplantation 2016; 100: 116-125.
10. Klintmalm GB, Feng S, Lake JR, et al. Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year

experience from a phase II randomized study. Am J Transplant 2014; 14: 1817-1827.
11. Neuberger JM, Bechstein WO, Kuypers DR, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. Transplantation 2017; 101: S1-S56.
12. Demetris AJ, Bellamy C, Hübscher SG, et al. 2016 Comprehensive update of the Banff Working Group on Liver Allograft Pathology: introduction of antibody-mediated rejection. Am J Transplant 2016; 16: 2816-2835.