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Original paper

Acute kidney injury in hospitalized patients with liver cirrhosis: real life use of the new proposed diagnostic criteria

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Abstract

Introduction: Acute kidney injury (AKI) in liver cirrhosis (ACLD) is frequent and associated with increased mortality; it could appear far earlier than full-blown hepatorenal syndrome (HRS) evolves. It was of much interest to the hepatology, therefore, when nephrologists begun to refine diagnostic criteria of what is currently known as AKI. Attempts to adopt it for patients with ACLD have led to widespread discussion; most controversies were related to leaving out of (already lowered) threshold creatininaemia (SCr) of 133 µmol/l for the definition of HRS type I. The ensuing new proposed diagnostic criteria for the AKI in ACLD have been in the process of external validation; therefore, studies from the real life clinical practice are of interest. The aim of this study was to investigate their applicability and prognostic validity in the cohort of hospitalized patients with decompensated ACLD (dACLD).

Material and methods: Retrospective study of consecutive admissions to tertiary referral liver unit. Inclusion criteria: hospital admission with dACLD; exclusion criteria: malignancy other than HCC, lack of data for analysis. Study interval: January 1st, 2013 – September 30th, 2013. Definitions: AKI – the new proposed criteria according to International Club of Ascites (ICA-AKI); chronic kidney disease (CKD) was defined according to KDIGO criteria.

Results: During study interval of 9 months, 326 patients with dACLD were admitted; females – 38%, mean age – 53 years (y), MELD – 16.5, ascites (CiA) – 47%. Etiology of dACLD: alcoholic liver disease (ALD) – 55%. AKI was diagnosed in 26% of dACLD admissions; AKI – stage 1 in 14%, AKI – stage 2 in 6%, and AKI – stage 3 in 6%, respectively. CKD, present in 26%, was the risk-factor for AKI. In-hospital mortality was 21% in AKI vs. 1% in non-AKI group, respectively ($p < 0.0001$); in AKI-1a (SCr < 133 µmol/l) 2.6%, AKI-1b 21.2% ($p = 0.01$). Complications were recorded in 39% of patients with AKI vs. 7% in non-AKI group, respectively ($p < 0.0001$); AKI-1a – 21%, AKI-1b – 33% ($p = 0.24$).

Conclusions: This study has shown that new proposed diagnostic criteria for AKI in patients with dACLD are applicable in daily clinical practice outside the context of clinical trials. The main significance of adopting new diagnostic criteria dwells in refined prognostic stratification of patients with dACLD, earlier introduction of volum-expansion with albumin, earlier introduction of terlipressin if albumin alone does not lead to improvement of AKI, and more personalized approach. In this study AKI-1a with SCr of < 133 µmol/l was associated with complications, but not with mortality.

Key words: liver cirrhosis, advanced chronic liver disease, acute kidney injury, diagnostic criteria.

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Introduction

In 2012, the estimated worldwide toll of acute kidney injury (AKI) would be 3 million deaths [1-3]. Every other patient admitted to intensive care unit (ICU) develop AKI, and 27% die before hospital discharge (four times that of patients without AKI) [3-6]. In liver cirrhosis, nowadays in clinical practice called advanced chronic liver disease (ACLD), AKI is frequent and deadly [4]. On admission, it is present in 19-32% of patients with dACLD (community-acquired AKI), and in 52% if acute chronic liver failure (ACLF) is present; the mortality of AKI stages 1, 2 and 3 is around 15%, 30%, and 60%, respectively [7-9].

The diagnostic criteria and management of AKI in ACLD are being under epochal transformation [10-12].

Although the term 'hepatorenal syndrome' (HRS) was already used in the first-third of 20th century, so-called 'traditional diagnostic criteria' were established only in 1996 and updated in 2007. In between, in 1959, Papper has described extreme renal vasoconstriction; in 1963, Flint published first description of the syndrome; in 1970, Epsteins' photographs of renal angiography pre- and post-mortem flew around the world, and in 1975, Rodes divided kidney injury into three types [13-20]. Acute renal failure (ARF), the term predecessing AKI, was defined as the increase of serum creatinine (sCr) level of ≥ 50% from baseline and to ≥ 133 μmol/l [13, 19]. These diagnostic criteria have been a strong predictor of in-hospital mortality, and have had a high specificity, but suffered from low sensitivity leading to late diagnosis and limited response to treatment in some patients [21-24]. Meanwhile, researchers as well as clinicians have recognized weaknesses of all three cornerstones of traditional diagnostic criteria for ARF in ACLD: threshold creatininaemia, timeframe of change in sCr, and sCr itself – as a biomarker of renal function [10, 11].

1. The use of diagnostic threshold for ARF/AKI in ACLD (sCr ≥ 133 μmol/l) has been supported by strong evidence that it predicts progression of AKI and prognosis of patients [7, 25]. However, the threshold had serious limitations: i) AKI was diagnosed in relatively late stage, hence could be less responsive to the therapy [8]; ii) it does not take into account changes over days to weeks to discern AKI from chronic kidney disease (CKD); iii) AKI with sCr < 133 μmol/l decreased survival in the cases: a) precipitated by infection (i-AKI), b) progressing, and c) of community-acquired AKI [26-30].
2. Timeframe used for diagnosing ARF/AKI in ACLD, except for HRS 1, often does not allow for unequivocal distinction between AKI and CKD. This point relates closely to the definition of baseline sCr, which if strict (i.e., 7 days, 14 days etc.), is destined to be underused in real-life clinical practice, where it is often unavailable.
3. Last but not least, there is a problem of sCr as a biomarker of renal function in general and in ACLD in particular: it is influenced by age, gender, sarcopenia, increased tubular secretion of creatinine, increased volume of distribution, interference of bilirubin with assays, etc. [31-33]. Overall, in ACLD, sCr overestimates projected glomerular filtration rate (eGFR) or kidney function [10, 11].

These drawbacks have fueled endeavors to redefine ARF in general population. Two separate bodies developed two consensus definitions of AKI (the term ARF was officially abandoned): the Acute Dialysis Quality Initiative group issued so-called RIFLE criteria (Risk, Injury, Failure, End-stage renal disease), and the Acute Kidney Injury Network (AKIN), so-called AKIN criteria of AKI [34-36]. Subsequently, panel of experts has suggested combining these two sets of criteria into unifying KDIGO criteria for AKI (the Kidney Disease Improving Global Outcome) [35]. These criteria were then tested in patients with ACLD and discussed on the Venice Convention of International Club of Ascites (ICA) in 2012; the discussion continued until April 2015, when experts agreed on the final proposal of a new approach to the diagnosis and therapy of AKI in cirrhosis (new proposed criteria) [7, 25, 27-29, 37-40]. The main difference from traditional criteria was the abandonment of fixed thresholds of sCr ≥ 133 μmol/l and > 221 μmol/l for AKI and HRS-1, respectively (Table 1); this is important, since the higher sCr, the lower the probability of response to terlipressin with albumin [41, 42]. Proof of concept for the new proposed criteria has been provided by their ability to predict mortality in various settings: i) in hospitalized patients with liver cirrhosis including those on ICU [7, 25, 27, 29, 38-40, 43-45]; ii) in cases of AKI with progression [7, 25, 39]; iii) in AKI grade 2 and 3 [7, 25, 39]; iv) in AKI with the highest sCr < 133 μmol/l (AKI-1a) [29, 30]; v) in outpatients with resolution of AKI [27]. The main lesson learnt from the application of the new proposed criteria was that even small increase in sCr should be identified for potentially early intervention. Only recommendation for treatment with vasoconstrictors of AKI-1a without change after volumexpansion with albumin requires more investigation [10, 11, 26]. The new proposed criteria do not eliminate the possibility of parenchymal renal disease in HRS; however, the potential role of urinary biomarkers in this setting is still unclear [7, 39, 46]. Response to therapy is classified as full, partial, and none with prognostic implications [47].

Table 1. International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of acute kidney injury (AKI) in patients with cirrhosis [10, 11]

Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr ⩾ 0.3 mg/dl (⩾ 26.5 µmol/l) within 48 hours; or, • A percentage increase sCr ⩾ 50% from baseline which is known, or presumed, to have occurred within the prior 7 days		
Staging of AKI	• **Stage 1**: increase in sCr ⩾ 0.3 mg/dl (26.5 µmol/l) or an increase in sCr ⩾ 1.5-fold to 2-fold from baseline • **Stage 2**: increase in sCr > 2-fold to 3-fold from baseline • **Stage 3**: increase of sCr > 3-fold from baseline or sCr ⩾ 4.0 mg/dl (353.6 µmol/l) with an acute increase ⩾ 0.3 mg/dl (26.5 µmol/l) or initiation of renal replacement therapy		
Progression of AKI	**Progression** Progression of AKI to a higher stage and/or need for RRT		**Regression** Regression of AKI to a lower stage
Response to treatment	**No response** No regression of AKI	**Partial response** Regression of AKI stage with a reduction of sCr to ⩾ 0.3 mg/dl (26.5 µmol/l) above the baseline value	**Full response** Return of sCr to a value within 0.3 mg/dl (26.5 µmol/l) of the baseline value

The aim of the study was to investigate the applicability and prognostic relevance of the new proposed ICA-AKI diagnostic criteria in real-life clinical setting.

Material and methods

Single center study at the division of Hepatology, Gastroenterology, and Liver Transplantation (HEGITO) of the Department of Internal Medicine in the Regional Teaching Hospital. Retrospective analysis of database 'HEGITO 7', which collects data of patients hospitalized with ACLD. Inclusion criteria: hospital admission for (dACLD); exclusion criteria: malignancy other than HCC, lack of data for analysis. Study interval: January 1st, 2013 – September 30th, 2013. As definitions for AKI and CKD, ICA-AKI and KDIGO criteria were used, respectively (Table 1) [10, 11, 35]. As a baseline sCr for diagnosis of AKI, values on admission or < 3 months prior to admission have been used. These were related to further three of sCr readings during hospitalization: minimal, maximal, and at discharge. Other recorded variables: age, gender, etiology of dACLD, drugs used before admission (specifically furosemide, spironolactone, angiotensin converting enzyme inhibitors and sartans), model for end stage liver disease (MELD), in-hospital mortality, complications of ACLD: ascites, as defined by [48], infections [49], variceal bleeding, hepatic encephalopathy [50], and length of hospital stay (LOS). Management of AKI followed traditional criteria and EASL guidelines of 2010 [48]. Notably, patients hospitalized for dACLD with AKI on admission have received volumexpansion with crystalloids and albumin 20%; those with HRS-1 with albumin 20% plus terlipressin after 48 hours in albumin non-responders. The administration of terlipressin was intravenous boluses q6h, in doses according to body weight: 1 mg or 2 mg in patients with < or > 70 kg, respectively [4, 5, 17]. Primary endpoints: prevalence of AKI according to new proposed criteria, in-hospital mortality related to AKI stages. Secondary endpoints: association of AKI with complications and LOS; differences between AKI-1a and -1b. Statistical analysis: descriptive, parametric variables were summarized by mean and standard deviation, and compared by Student's *t*-test, categorical variables were compared using χ^2 test. Two-sided null hypotheses of no difference were rejected if *p*-values were less than 0.05. Cases with missing data were allowed zero value or discarded from analysis.

Results

From 972 hospitalizations during study interval of 9 months, 326 were for dACLD (33%) (Table 2); females – 123 (37.7%); mean age – 53 years (19-85); MELD – 16.5 (6.6-46.7); ascites – 155 (47.5%); HCC – 21 (6.4%); laboratory values on admission: albumin – 31.8 ± 6.9 g/l; bilirubin – 86.6 µmol/l (4.7-670.6); sCr – 103.5 µmol/l (37-609); international normalized ratio (INR) – 1.51 ± 0.36; prothrombin time (Quick, PT) – 52 ± 14.5%. Etiology of dACLD: alcoholic liver disease (ALD) 179 (54.9%); primary biliary and sclerosing cholangitis (PBC + PSC) 26 (8%); hepatitis B and C viral infection (HBV + HCV) 24 (7.3%). AKI was diagnosed in 110 of 326 cases (33.7%); AKI-1 in 71 (21.7%), AKI-2 in 19 (5.8%), and AKI-3 in 20 cases (6.1%). MELD scores calculated on admission in AKI vs. non-AKI groups were 21.8 (8.2-46.7) vs. 14.6 (6.2-43.1) ($p < 0.0001$); MELD in AKI-1a vs. AKI-1b were 17.4 (8.4-36.8) vs. 23.1

Table 2. Prevalence of acute kidney injury according to baseline demographic and clinical variables (n = 326)

Variable	No AKI	AKI	p
Number of patients	242	84	
Age (years)	53.9	54.4	n.s.
Gender female (%)	26.7	11	n.s.
ALD (%)	67	33	0.001
Viral hepatitis B + C (%)	88	13	
Other etiologies (%)	84	16	
MELD score (points)	14.6	21.8	0.0004

AKI – acute kidney injury, MELD – model for end stage liver disease, ALD – alcoholic liver disease

(10.4-40.2) (p = 0.0076). AKI was more prevalent in ALD as compared to both viral, and other etiologies of ACLD (33%, 12%, 16%, respectively; p = 0.001). In-hospital mortality (n = 216) (Fig. 1): there were 20 deaths in AKI (21%), and 2 (1%) in non-AKI groups, respectively (p < 0.0001); mortality in AKI subgroups: AKI-1 – 8/61 (13.1%) (AKI-1a – 1/38 (2.6%), AKI-1b – 7/33 (21.2%), p = 0.01), AKI-2 – 4/19 (21.0%) (p vs. AKI-1b = 0.99), AKI-3 – 11/20 (55%) (p vs. AKI-2 = 0.03, p vs. non-AKI = 0.00001). Complications (Fig. 2): frequency in AKI vs. non-AKI group was 43/110 (39%) vs. 16/216 (7.4%) (p < 0.0001); in AKI-1 – 19/71 (26.7%) (AKI-1a 8/38 (21.1%), AKI 1b 11/33 (33%) (p = 0.24), in AKI-2 – 12/19 (63%) (p vs. AKI-1b = 0.04), in AKI-3 – 11/20 (60%) (p vs. non-AKI = 0.000001, p vs. AKI-2 = 0.84). Mean LOS in whole cohort was 9.5 days (1-45) (Fig. 3). LOS in non-AKI vs. AKI were 6.8 days (1-34) vs. 14.7 days (0-45) (p < 0.0001); in AKI-1 LOS was 12.3 days (AKI-1a – 12.4 days, AKI-1b – 12.1 days) (p = 0.88), in AKI-2 – 17.6 days (p vs. AKI-1b = 0.003), AKI-3 20.9 days (p vs. non-AKI = 0.000001, p vs. AKI-2 = 0.0005). CKD on admission: overall – 86/326 (26.4%), grade 2 (G2) – 58 (17.8%), grade 3 (G3) – 21 (6.4%), grade 4 (G4) – 6 (1.8%), grade 5 (G5) 1 (0.3%). In CKD ≤ G2 as compared to CKD > 2, the frequency of AKI was 23.8% (71/298) vs. 46.4% (13/28) (p = 0.009).

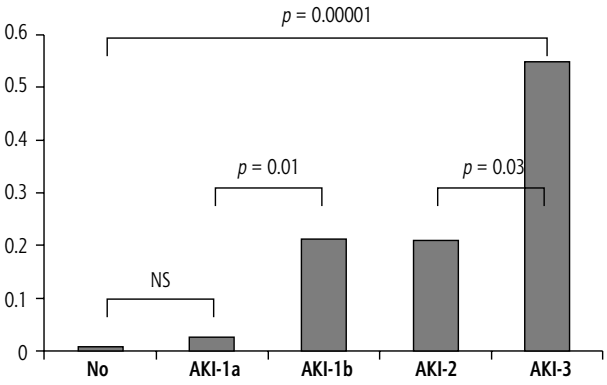

Fig 1. Mortality according to acute kidney injury (AKI) grades (n = 326)

Discussion

As in several other papers on the topic, results of current study support the case for implementing the new proposed ICA-AKI criteria into daily clinical practice. Thanks to these criteria, even small changes in sCr – otherwise often left unrecognized due mainly to low baseline sCr in patients with ACLD – are being classified and, more importantly, treated as AKI [8, 25, 27-29, 37, 39, 40].

One-in-four prevalence of AKI in our patients hospitalized with dACLD compares well with 19-47% from other studies, as does its 14% – 6% – 6% distribution of AKI grades 1, 2, and 3. Lower age (51 years) and more ALD etiology of ACLD in our study are beyond the scope of discussion, since between-studies comparison of mortality and complications were not intended. It is apparent from the results, that the probability of AKI is etiology-of-ACLD – sensitive, with significantly higher prevalence in ALD than other etiologies. The most important finding has been the association of AKI ≥ 1b

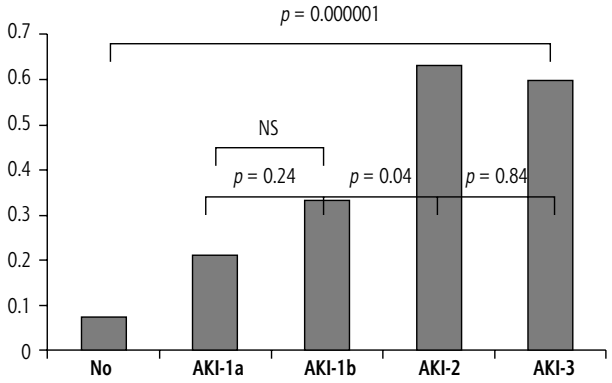

Fig 2. Complications according to acute kidney injury (AKI) grades (n = 326)

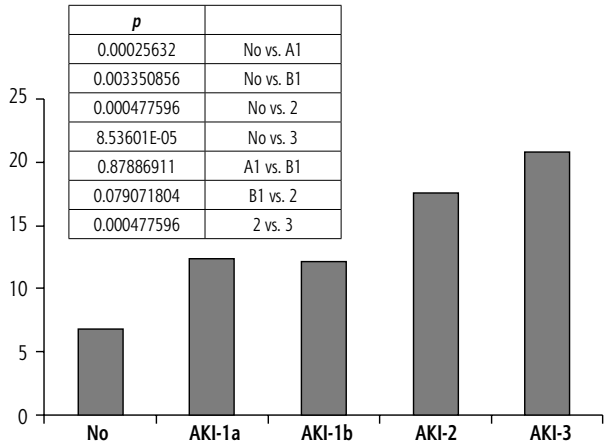

Fig 3. Length of hospital stay (days) (n = 326)

with mortality (Fig. 1); notably, more than 50% of patients with AKI-3 has died. On the other hand, similar mortality of patients with AKI-1a as compared to patients without AKI could be seen as the argument against the abandonment of threshold sCr of 133 μmol/l (1.5 mg/dl) [12, 51]. However, significantly higher complications (Fig. 2) in AKI-1a as compared to non-AKI group, allows for an alternative explanation: recognizing the earliest AKI stage leads to more sensitive approach to all the other complications of ACLD, their earlier recognition, more intense therapy, and reduction in mortality; the association of AKI-1a with complications is real and has been also supported by LOS, which was almost twice as high as in patients without AKI (Fig. 3). Of interest was 26% prevalence of CKD at admission; AKI was present in half the patients with CKD ≤ 2, as compared to CKD grade > 2; CKD should therefore be scrutinized as the possible risk factor for AKI.

This study suffers several limitations. Bias introduced by its retrospective design was somewhat mitigated by the fact that in-hospital data has been collected over the span of the study in standardized and supervised manner (JV). The design has not allowed for distinguishing nosocomial AKI from community-acquired. Number of patients, although limited, has not precluded main conclusions concerning mortality, but could have influenced secondary endpoints, particularly differences between AKI-1a and 1b. Impossibility to retrieve detailed information on management, specifically the exact type and dose of volumexpanders, and the threshold for addition of terlipressin; this precluded the retrospective diagnosis of HRS, which is one of the major drawbacks of the study. However, according to the recent analysis of 300 patients with cirrhosis and AKI from Italy and Spain, the distribution of HRS among AKI stages 1-3 has been shown to be even; the main results of our study would stay unchanged [52].

The aim of this study was to investigate in real-life clinical practice the feasibility and relevance of the new proposed diagnostic criteria for AKI in ACLD shortly after their announcement in 2011 (the Berlin 2011 ICA-EASL Joint Meeting [Renal Dysfunction in Cirrhosis in the era of AKI: towards a new definition]) [26]. The results lend support to the lowering of threshold for the diagnosis of AKI. Even in its earliest stages, AKI is associated with worse outcome. It will be of interest to see the general impact of the new proposed diagnostic criteria on the outcome in the ACLD cohort, since they could lead to earlier interventions.

Conclusions

The new proposed diagnostic criteria of ICA-AKI are applicable in ACLD patients from real-life clinical practice. They were of immediate clinical relevance, since AKI of all stages was associated with complications and LOS. Mortality was associated only with AKI stages 1b and higher. As to the controversy surrounding AKI-1a, our results are difficult to interpret; for the abovementioned reasons, however, authors will retain AKI-1a as the stage most amenable to interventions with the probability of preventing fatal outcomes.

Disclosure

Authors report no conflict of interest.

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Review paper

Acute-over-chronic liver failure (ACLF) – immunity, infection, inflammation

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Abstract

The syndrome of acute-over-chronic liver failure (ACLF) was described in the landmark CANONIC study as the process resulting from the acute insult to the pre-existing chronic liver disease (ACLD, cirrhosis) with consequent failures of the liver, kidneys, circulation, lungs, and hemostasis; all of them were diagnosed by CLIF-modified SOFA scores, nowadays available as an internet calculator. Similarly determined by the study results, was the characteristically high short-term mortality of ACLF. Subsequent studies, although heterogeneous due to the differences of the diagnostic criteria of Europe, USA, and Asia, brought about the proof-of-concept with additional important findings on the dynamics of the syndrome, during the first days of clinical presentation, as well as the close pathophysiological link between ACLF, immunity, inflammation, and infections. The background immunological milieu of ACLD is that of immune deficit (CAIDS), gut dysbiosis, leaky gut, and chronic systemic low-grade inflammation. Most of the hits (triggers), which use to convert ACLD to ACLF are inflammatory in nature, as is the response of organism. The prevailing immunological status truncate prognosis into fulminant death, early recovery, recovery due to intervention in the golden window, the catabolic draw of PICS, and indolent death. Although the therapeutic interventions are mostly non-specific, their intensive implementation can lead to improvement in the survival in all the categories of ACLF. Immunity, inflammation, and infections are in the focus of current scientific interest; ligands and receptors of known pathways, gut microbiome, gut barrier, and bacteria are the main therapeutic targets. Liver regeneration, liver replacement, and futility are another hot topics of ACLF research. Until its results become available, the cornerstones of management of ACLF will remain based on the adherence to the basic principles – early diagnosis, management on ICU, emphasis on infections and inflammation, early prognostic re-stratification, and previously tough decisions about liver replacement/regeneration, and futility.

Key words: acute-over-chronic liver failure, immunity, inflammation, infection, management.

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Introduction

The syndrome named ACLF (acute-over-chronic liver failure) has relatively short history. In 1995, it was mentioned by Ohnishi; in 2002, a dedicated working party was organized in London; in 2009, Chronic Liver Failure (CLIF) Consortium was created, whose endeavor led to the landmark study on ACLF in 2013. The CANONIC study set the scene for the introduction of ACLF to clinical practice [1]. Ever since, CLIF Consortium, European Association for the Study of the Liver (EASL) (jointly EASL-CLIF), Asian Pacific Association for the Study of the Liver (APASL), North American Consortium for the Study of End-Stage Liver Disease (NACSELD), and several other bodies have striven for unifying diagnostic criteria, which were consented in 2014 [1-7]. The main question fueling the debate around the diagnostic criteria has been the necessity (or not) of the clear-cut liver cirrhosis as the background stage of the underlying liver disease. This problem was indirectly mitigated by the Baveno VI recommendation to coin the term 'advanced chronic liver disease' (ACLD), rather than cirrhosis [5, 8]. From the 15% new decompensations per year of previously

asymptomatic ACLD, ACLF was present in around 25% at admission, and developed in another 10% during hospitalization; therefore, ACLF can be considered a common entity [1, 4, 9-14].

At least in the medical environment proximate to the authors, there has been noticeable hesitation to accept ACLF as a self-existing entity. One may and probably should ask: why? One explanation could be that the abyss lying between the toll ACLF claims on the one side, and the lack of disease-specific therapy on the other, creates environment of hopelessness and frustration, leading to evasive behavior. This causal cascade, operative in the ACLF arena for years, has been accompanied by the increasing money-sensitivity of medical care: the almost prohibitive cost per life saved could be but understandable hindrance. The cost at the intensive care unit (ICU) can be as high as 50,000 £, one hospitalization could reach up to 116-180 $, and one year expenditures – 3 billion $ [15, 16]. The admission of patient with acute decompensation (AD) to ICU means green-light for giving out the money. On the other hand, turning blind eye means nobody would care, because patients with decompensated (d)ACLD simply use to die, and there is no specific therapy for possible ACLF anyway. However, this standpoint cannot be accepted anymore. First, there is an ontological reason. Only acceptance of the limitations could lead to the brainstorming necessary for progress. Two studies have already shown how mere admission to the ICU has led to decrease in mortality and improvement of survival [17, 18]; the new pathophysiological paradigm – 'from peripheral arterial vasodilation to systemic inflammation hypothesis' – has been formulated [19], and new treatment options are on the horizon (see below).

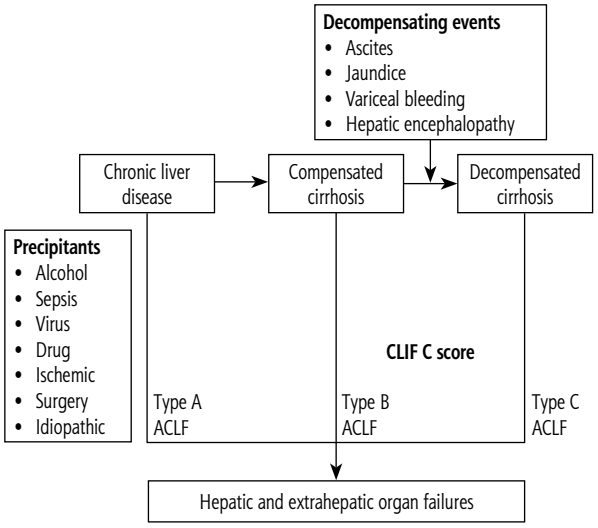


Fig. 1. Subtypes of acute-over-chronic liver failure (ACLF) [5]

Diagnosis and prognosis

Definition

In the CANONIC study, ACLF was defined as AD of liver cirrhosis associated with organ/system failure(s), which may develop any time during the course of the disease, and is associated to a short-term (28-day) mortality, ranging from 23% to 74%, depending on the number of organ failures [1]. Currently, ACLF is defined as an acute deterioration of preexisting, chronic liver disease (with or without the presence of liver cirrhosis), due to a precipitating event with additional failure of one or more organs or systems, and associated with high short-term mortality [7, 10]. Despite evidence-based definition and diagnostic criteria, ACLF population remains heterogenous [20].

Timeframe

The first step to the diagnosis of ACLF in patients with dACLD is the determination of its duration: ACLF should be suspected in each patient with AD, defined as the appearance of the decompensating event 2-4 weeks before admission [20]. Because ACLF is a very dynamic process, it is recommended to re-calculate its grade once more anytime 3 to 7 days after the diagnosis, since at this point, 81% of patients achieve their final ACLF grade, and this grade predicts mortality better than that at admission (see below) [21, 22].

Decompensating events (Fig. 1)

All the so-called specific complications of ACLD are to be considered the potential decompensating events, by which ACLF presents itself: i.e., ascites, jaundice, portal hypertensive bleeding, hepatic encephalopathy (HE), and bacterial infections. If the first ever decompensating event is full-blown ACLF, the mortality is higher than in patients with the history of previous decompensations [1]. The role of the etiology of underlying ACLD was the focus of interest in at least eight studies, summarized by Abbas *et al.* [23, 24].

Diagnostic criteria

Diagnostic criteria are based on three domains: 1) AD of 2) ACLD with 3) organ/system failure(s). Currently, provided the presence of clinical suspicion, diagnosis of ACLF is easy: all the patients admitted to the hospital with AD (timeframe + decompensating events) should be examined for the presence of ACLF by uploading their clinical and laboratory variables into

Table 1. CLIF-OF scoring system for diagnosing acute over chronic liver failure (ACLF) [5]

Organ system	Score = 1	Score = 2	Score = 3
Liver: bilirubin (mg/dl)	< 6.0	⩽ 6.0-12.0	> 12.0
Kidney: creatinine (mg/dl)	< 2.0	⩾ 2.0 – < 3.5	⩾ 3.5 or renal replacement therapy
Cerebral: HE grade	Grade 0	Grade 1-2	Grade 3-4
Coagulation: INR	< 2	> 2.0-2.5	⩾ 2.5
Circulation: MAP (mmHg)	⩾ 70 mmHg	< 70 mmHg	Vasopressors
Respiratory: PaO_2/FiO_2 or SpO_2/FiO_2)	> 300 > 357	> 200 – ⩽ 300 > 214 – ⩽ 357	⩽ 200 ⩽ 214

HE – hepatic encephalopathy, INR – international normalised ratio, MAP – mean arterial pressure, PaO_2 – arterial partial pressure of oxygen, SpO_2 – oxygen saturation, FiO_2 – fraction of inspired oxygen

Table 2. Acute over chronic liver failure (ACLF) grades and prognosis [86]

	No ACLF	ACLF grade 1	ACLF grade 2	ACLF grade 3
Definitions ACLF	1) No organ failure 2) Single organ failure (liver, coagulation, circulation, lungs) in patients with serum creatinine levels < 133 mmol/l and no hepatic encephalopathy 3) Single cerebral failure in patients with serum creatinine levels < 133 mmol/l	1) Single kidney failure 2) Single organ failure in patients with serum creatinine levels ranging from 133 mmol/l to 176 mmol/l and/or grade 1-2 hepatic encephalopathy 3) Single cerebral failure with serum creatinine from 133 mmol/l to 176 mmol/l	Defined by the presence of two organ failures	Defined by the presence of three organ failures or more
28-day and 90-day mortality rate (%)	4.7; 14.0	22.1; 40.7	32.0; 52.3	76.7; 79.1

the freely available web-calculator (www.clifresearch.com/ToolsCalculators.aspx) [11]. As mentioned, coining the term ACLD instead of cirrhosis also contributed to simplification of the diagnostic process [8]. i) The original (West) diagnostic criteria issued by the CANONIC study were based on the presence of liver cirrhosis, AD, and organ/system failures determined by CLIF-modified Sequential Organ Failure Score (CLIF-SOFA) [1] (Table 1). ii) The APASL (East) criteria have broadened the cohort by the (abundant in the East) patients without liver cirrhosis, and excerpted the hepatic from the insults, as well as ascites and HE from events [2, 3]. iii) Unifying consensus definition resolved some of the issues by dividing the syndrome to types A-C (Fig. 1) [5]. The quantitative influence on mortality of all the individual organ-, and system-failures included in CLIF-SOFA scoring system, i.e., the liver, coagulation, kidney, circulation, brain, and lung, was subsequently revised [25]. Therefore, patients with single organ failure are not automatically included to ACLF 1; rather, according to the organ involved, they were divided into ACLF 1a, and 1b. Apart from confirming the presence (or absence) of the ACLF, web calculator also displays the probability of 28-day mortality (Fig. 2) and, after uploading the age and white blood cells count (WBC), the calculator offers additional refinement of prognosis in patients with AD.

Precipitating events

Precipitating events (insults, triggers) are detectable in two-thirds to 50% of cases [1]. The knowledge of their local representation allows for the comparison of cohorts and built-up of prevention [26]. On the other hand, knowing the precipitating event of an in-

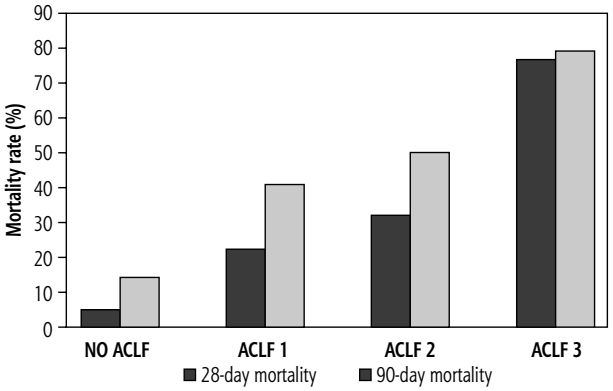


Fig. 2. Survival according to the acute over chronic liver failure (ACLF) grade [1]

dividual patient, further refines his or her prognostic stratification and enables personalized approach; intrahepatic events bear poorer prognosis than extrahepatic [13].Therefore, the division of events to extrahepatic (bleeding, infection, surgery etc.) and intrahepatic (e.g., flares of chronic hepatitis B, autoimmune hepatitis, Wilson's disease; superinfection by hepatitis A, or hepatitis E virus infection, acute alcoholic hepatitis, drug-induced liver injury, etc.), is of prognostic importance. Of note, large-volume paracentesis without albumin replacement is one of the listed triggers [24]. In Western countries, ACLF usually occurs in a context of systemic inflammatory response syndrome (SIRS) due to severe alcoholic hepatitis, bacterial infection, or to unknown causes suspected of bearing the relation to the gut-liver axis [1, 4].

Time-course

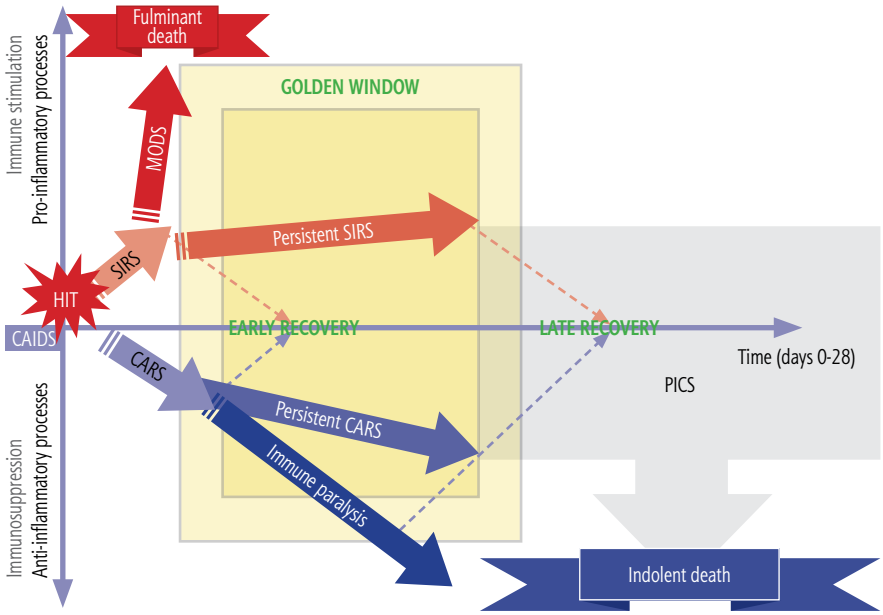
One of the hallmarks of ACLF is its dynamic nature; the changes (for better or worse) in ACLF grades have occurred very rapidly, rapidly, or slowly in 40%, 15%, and 15% of the patients, respectively [21]. The evolution of the ACLF grades between the two time-points (1 – at admission, 2 – at any time from day 3 to day 7), gives the additional prognostic information over the ACLF grade at admission; the ACLF grade at the 2nd time-point has been termed 'final ACLF' [21]. The 28-day mortality of the final ACLF1 has been worse than that of the resolved ACLF (18% vs. 6%), but distinctively better than that of the final ACLF 2-3 (42-92%) [21]. This lends support to the case for the so-called 'golden window', or 'window of opportunity' (for the intervention to be most effective) coined by Sarin [27, 28]. The resolution of ACLF could be achieved in around 40% (53%, 35%, and 16% for the ACLF grades 1, 2, and 3, respectively), and was accompanied by low short-term mortality (6%), as compared to the unresolved ACLF (18%) [21]. Another consequence of the first-week dynamics is the subdivision of ACLF to the severe early course (final ACLF > 1), and non-severe early course (final ACLF ≤ 1) [21]. The severe early course cohort seems to be sufficiently homogenous and enriched for the study of therapeutic measures [29, 30]. Half the patients with severe early course were progressed from ACLF 1, 45% were non-movers, and 5% were improvers from ACLF 3 to ACLF 2 [21].

Inflammation and ACLF

Whereas the liver has tendency to establish immune tolerance, one of the most prominent features of ACLF has been the escalated systemic inflammation [24, 31]. The situation is further complicated by the fact that ACLF is evolving in the setting of chronic immune dysfunction and low-grade inflammation of ACLD, known as cirrhosis-associated immune dysfunction syndrome (CAIDS) [32]. It was the very strength of the association between the degree of liver injury and immune deficit, and relatively standard structure of immune derangements in CAIDS, which rendered infections specific complications of ACLD [28, 33].

Pro-inflammatory state (SIRS) of ACLF can itself be robust enough to kill [34] (Fig. 3). Ignited mainly by the early innate immune response, SIRS could be the dominant pathophysiological basis of the multiorgan failure (MOF) and death, termed in this case as 'fulminant death' (Fig. 3) [35]. Subsequently, SIRS is counterbalanced by compensatory anti-inflammatory response syndrome (CARS) [36]. The main purpose of CARS is beneficial – to prevent autogenous damage to the organs and tissues by the excessive inflammation [36]. To quote from the Rosenthal *et al.* "...while SIRS was a pro-inflammatory syndrome that seemed tasked with killing infectious organisms through activation of the immune system, CARS was a systemic deactivation of the immune system tasked with restoring homeostasis from an inflammatory state" [35]. There are two situations, however, in which CARS can turn detrimental: if its intensity overbalances SIRS so much that the result is the so-called immune paralysis, or if the length of duration of SIRS-CARS co-existence leads to the exhaustion of immune and energy reserves with catabolic state called persistent inflammatory, immunosuppressed, catabolic syndrome (PICS) [35]. Some authors call these patients chronically critically ill [37]. One way or another, CARS is setting the stage for late nosocomial infections that can precipitate late-onset MOF, and the so-called 'indolent death' (Fig. 3) [36, 38, 39]. Molecular and cellular mechanisms behind CAIDS, SIRS, CARS, and PICS were described elsewhere [34-36, 38-41].

There are two inflammatory contexts of ACLF: with and without infection [24]. The first, infection-associated, represents at least 30% of the burden, and has been designated (by NACSELD) as iACLF [4, 42-44]. Infection was the offence in 38-80% of all ACLF cases [1, 11, 13], and even more significant if they were of nosocomial origin [12]. In submitted study by Fernandez *et al.*, referred at the International Liver Congress 2017, 25% and 37% of patients with AD and ACLF had infection at admission, respectively. In non-infected patients from the same study, 18%, 37%, 47%, and 81% acquired bacterial infections during the course of AD, ACLF 1, ACLF 2, and ACLF 3, respectively. That ACLF is the risk factor for acquisition of infections – with



PICS – persistent inflammatory, immunosuppressed, catabolic syndrome, MOF – multiple organ failure, SIRS – systemic inflammatory response syndrome, CARS – compensatory anti-inflammatory response syndrome

Fig. 3. Acute over chronic liver failure (ACLF) and inflammatory responses [35]

the frequency twice as high as in chronic liver failure (58% vs. 26%, $p = 0.007$) was shown in the study by Katoonizadeh [45]. Bacteria trigger inflammation by their PAMPs (pattern associated molecular patterns), or by their virulence factors, both of which engage PRRs (pattern recognition receptors), and launch the so-called structural feature recognition [24]. The most well-known PRRs is toll-like receptor (TLR) family, present on the innate-immunity and epithelial cells. Receptors for ligands of other microorganisms, such as viruses and fungi, are different from those of bacteria. Mortality in bacterial sepsis is higher in patients with cirrhosis than without, and the second infection in one ACLF multiplies the mortality [43, 46].

The inflammatory phenotype of ACLF without infection is characterized by elevated levels of pro-inflammatory markers such as WBC, C-reactive protein, interleukin (IL)-6, IL-1β, and IL-8 [41, 47, 48]. The prototype of non-infectious inflammatory ACLF phenotype is acute alcoholic hepatitis. Inflammation in non-infectious context is triggered by the released content of damaged cells, or broken-down extracellular matrix [24, 49-51]. Together, they are known as danger-associated molecular patterns (DAMPs), and are – with their respective receptors – listed in the review by Hernaez *et al.* [24]. If the trigger of inflammation is not identifiable, three possible sources are postulated: changed microbiota with translocated metabolites of gut bacteria, translocated PAMPs of gut bacteria, and DAMPs [4, 52-54].

Management

There is no specific treatment of ACLF available [55, 56]. As already mentioned, mortality can be decreased by admitting all the ACLF patients to the ICU, presumed cost notwithstanding. It is important to strive to hit the golden window, the timeframe of opportunity for SIRS-CARS tension to be lessened before one of them will prevail in either fulminant or indolent death; or, before their prolonged draw will cause PICS. In fact, they are exactly patients with PICS who drain the most of the resources, with enthusiasm for ACLF included. The basic principles of the management of ACLF could be summarized as follows:

1. Early diagnosis by extracting AD from dACLD, uploading variables to clifresearch.com.
2. Prognostic stratification of ACLF at days 0 and 7 with the
   a) final ACLF, and
   b) non/severe early course as the bases for decision-making.
3. Intensive care and clinical nutrition, aimed at the improvement of organ failures present at the diagnosis, and prevention of the impairment of other organs during hospitalization [9, 57].
4. Combatting bacterial infections by hitting fast and hard in the empirical interval by choosing the most powerful, broadest-spectrum antibiotics according to the actual hospital epidemiology/microbiology results [58]. In the long-term, the cornerstones of

success is the evidence-based antibiotic stewardship [59, 60]. If the insult is new-onset (e.g., hepatitis E) or flare-up (e.g., hepatitis B) of viral hepatitis, the therapy is straight forward.

5. Manipulation of the inflammation and immunity. Stimulation of the immunity has been investigated by some groups based on the premise that high-grade SIRS notwithstanding, the prevailing immune milieu during the golden window has been immune deficit, resulting from the combination of background CAIDS with CARS [41]. Growth factors for WBC (G-CSF) in 12-dose protocol, erythropoietin (in combination with G-CSF), or other non-specific immune stimulants such as transfer factor, has been all tested in pilot studies with promising results [61-64]. It has to be pointed out that both G-CFM and EPO were also perceived as the mediators of regeneration for hepatocytes [65, 66]. Microbiome and inflammasomes are another targets for immune manipulation, with rifaximin and some other antibiotics and drugs being studied as potential disease- modifying anti-cirrhotic drugs (DMACT) [67-71]. Anti-inflammatory measures are to be tested in the search for DMACTs (P. Caraceni, ILC® 2017). Solving their seemingly oxymoronous relationship with the immune-stimulating approaches is the area of intensive research [72]. One of the examples could be the treatment of acute alcoholic hepatitis [73-75].
6. 'Liver failure is the failure of liver regeneration' said the journal 'Science' in 1997. Suboptimal regeneration of hepatocytes is therapeutic target distilled from the deepening knowledge of the pathophysiology of liver failure, and ACLF [62, 76-78]. New hepatocytes are derived from the liver- or bone-marrow niches, respectively [79, 80]. Growth factors (G-CFM, EPO) mentioned above are one of possible mediators of regeneration. There were at least six and four studies on the augmentation of the liver regeneration, by the sorted and unsorted bone marrow-derived mononuclear cells, respectively [81]. Other possibilities are the hepatocyte transplantation and bioartificial liver.
7. Fast-track liver transplantation (LTx) in severe early course, especially in non-responders to therapy of ACLF, so-called salvage LTx, is the area of intensive study [82-85]. Since the prognosis of the severe early course ACLF is dismal (28-day mortality, 34-51%), LTx (1-year survival > 75%), aroused as the logical area to investigate. However, the uptakes of LTx in pivotal trials were only 2.2%, and 4.9%, and the waiting-list mortality more than 50% [21, 84, 85]. The prioritization on the waiting list (the sickest first?), timing of LTx (the sooner the better?), futility (too sick to be transplanted?), and net transplant benefit (the good for all?) are the areas of further research in ACLF [86, 87]. As for the too sick to be transplanted, proposed for confirmatory studies are ACLF points > 64, 3 organ supports, ACLF 3, respiratory failure, intensity of organ support (e.g., vasopressor dose), and the duration of organ support [88].
8. Liver support. Whereas general intensive care focuses on the support of the other organs and systems, liver support deals with the core organ of ACLF – the liver. So-called extracorporeal liver support systems (MARS, Prometheus) are the only more widely available modalities from this group, which were studied in two tens of dozens of patients with ACLF; none of the methods led to the improvement of overall survival [29, 30].
9. Never give up. Until the new studies will clearly show otherwise, or until informed and competent patient requests quitting AND the family requests to quit, AND the interdisciplinary team unequivocally consents that the probability of recovery is negligible, there is no other option than to continue therapy [21]. Studies in this area are underway.

Conclusions

ACLF is the syndrome with significant prevalence in patients admitted to the hospital with dACLD with distinct diagnostic features and high short-term mortality. It is worth uploading the few variables of the patients with AD to the web calculator and see if the criteria for ACLF are fulfilled. If they are, the patient should be admitted to the ICU. Since the core pathophysiology of the syndrome has much to do with immunity, inflammation, and infections, the most specific of current non-specific measures are directed their way, as is the research. Salvage LTx is the evidence-based option, but lot of issues remain to be resolved; who is too sick to be transplanted, and whose liver parenchyma could be helped to regenerate over the critical mass, are but the few.

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Programme and abstracts*

*The abstracts are printed in the form sent by authors, accepted by the Scientific Programme Committee.

Introductory word

The idea of Central European Hepatological Collaboration (CEHC) was developed during informal discussions between hepatologists from Czech Republic, Hungary, Poland and Slovakia in early 2015. The aim of CEHC is to find out the way of possible collaboration between physicians and medical scientists involved in educational and scientific activities related to liver diseases in the Central Europe. We already started research program on long term follow-up of HCV treatment with interferon-free regimens and we hope to begin shortly programs on the HCV screening and hepatic fibrosis. CEHC is also open for collaboration with hepatologists from other countries of the region. The first Meeting of the Initiative Group for Central European Hepatological Collaboration (CEHC) was very exclusive and attended by just eighteen representatives of hepatology associations/sections from the region and took place on 19-21 November 2015 in Warsaw. Further meetings were accompanied CELD Conference in Budapest (23-25 June 2016) and Academy of Contemporary Hepatology in Cracow (6-8 October 2016). The 9th Symposium on Portal Hypertension in Banská Štiavnica (16-17 June 2017) will be an excellent opportunity to meet again, present already available data and discuss further plans of hepatological collaboration in central Europe.

Prof. dr hab. med. Robert Flisiak

Dear colleagues,

we would like to invite you to the **9th Symposium on Portal Hypertension** (SPH-9) with the main topic **'The liver and infections'**. The relationship between infections and advanced chronic liver disease (ACLD) has been the hot topic, since infections are the cause or complication of up to 20-30% of ACLDs. Moreover, ACLD-infections connection has exceeded the limits of simple association, and is considered causal. This can be seen in the names of known syndromes (i-ACLF, i-AKI, CAIDS, etc.). To highlight its severity, the cirrhosis-associated immune dysfunction (CAID) was likened to AIDS by the name cirrhosis-associated immune deficit syndrome – CAIDS.

Fields of hepatitis B and C treatments are the preeminent examples of the potential of the translational medicine; hepatitis E virus stepped over its percieved geographical borders and should receive its standard role in the differential diagnostic considerations when it comes to acute or chronic hepatitis all around the Europe.

This year is very special for SPH because it was given the honour to host summit of the CEHC (Central European Hepatological Collaboration) organization. We hope that the meeting in the Old Castle will be the fertile ground for creating and strenghtening the perpersonal, professional and international relationships with the benefit for our patients.

We are looking forward to meeting you in Banská Štiavnica!

Lubomir Skladany
Svetlana Adamcova-Selčanová

Programme
9th Symposium on Portal Hypertension – The liver and infections

	Friday/Piatok, 16 June 2017
9.00-12.30	**CEHC meeting (Kammerhof)/*Zasadnutie CEHC***
12.30-14.00	**CEHC lunch (4 Sochy)**
14.00-18.00	**Open registration/*Registrácia otvorená***
15.00-15.25	**Sympózium firmy Astellas** *Clostridium difficile* infection in patients with ACLD and after liver transplantation/ *Infekcia Clostridium difficile u pacientov s ACLD (advanced chronic liver disease) a po transplantácii pečene* L. Gombošová (UPJŠ, Košice)
15.30-15.35	**Opening of the 9th Symposium on Portal Hypertension (SPH-9)/*Otvorenie 9. Sympózia o portálnej hypertenzii*** Predsedníctvo: Š. Hrušovsky – HO pre hepatológiu, I. Schréter – HO pre infektológiu Autori: Ľ. Skladaný (prezident SHS)
15.35-15.40	**Introduction from the President of Slovak Society of Infectology/*Slovo prezidenta SSI*** Pavol Jarčuška (prezident SSI)
15.45-17.30	**I. Blok CEHC** Predsedníctvo: R. Flisiak, B. Hunyady, P. Jarčuška, J. Šperl
15.45-16.00	Treatment of HCV infection in ACLD and after liver transplantation: The news/*Liečba HCV infekcie pri ACLD a po transplantácii pečene: Novinky* R. Flisiak (Department of Infectious Diseases and Hepatology, Medical University of Białystok, Poland)
16.00-16.15	Bacterial infections in ACLD: Review/*Bakteriálne infekcie pri ACLD: Review* B. Hunyady (Pécsi Tudományegyetem, Klinikai Központ, I.sz. Belgyógyászati Klinika, Hungary)
16.15-16.30	Role of serological markers in the diagnosis and prognosis of bacterial infection in cirrhosis/ *Úloha sérologických markerov pri diagnostike a prognóze bakteriálnych infekcií pri cirhóze pečene* M. Papp (University of Debrecen Clinical Centre, Institute of Internal Medicine, 2nd Department of Medicine)
16.30-16.45	Direct Acting Antiviral (DAA), hepatocellular carcinoma and HBV reactivation: Controversies/ *Priamo posobiace antivirotiká (DAA), hepatocelulárny karcinóm a reaktivácia HBV: Kontroverzie* J. Šperl (IKEM, Praha)
16.45-17.00	Albumin and infections in ACLD: update/*Albumín a infekcie pri ACLD: update* P. Jarčuška (UPJŠ, Košice)
17.00-17.10	Infections in ACLD: economic aspects/*Infekcie pri cirhóze: ekonomické aspekty* J. Lata (OU, Ostrava)
17.10-17.20	Antibiotic stewardship on the Liver Unit/*Na výsledkoch založené riadenie antibiotickej liečby v hepatológii* J. Šváč (FDR, Banská Bystrica)
17.20-17.30	**Discussion/*Diskusia***
17.30-17.45	**Coffee break**
17.45-19.00	**II. Blok** Predsedníctvo: S. Okapec, D. Pindák, P. Jarčuška
17.45-18.00	Microbiome in ACLD and infections/*Mikrobióm ACLD* L. Bajer (IKEM, Praha)
18.00-18.10	Rare fungal infections in patients with ACLD/CAID and after liver transplantation/ *Zriedkavé mykózy u pacientov s CAID a po tronsplantácii pečene* P. Jarčuška (UPJŠ, Košice)
18.10-18.20	Liver abscesses/*Abscesy pečene* M. Brunčák (FDR, Banská Bystrica)
18.20-18.30	Echinococcosis: the infectologist's view/*Echinokokóza z pohľadu infektológa* Z. Paraličová (UPJŠ, Košice)
18.30-18.40	Echinococcosis: the surgeon's view/*Echinokokóza z pohľadu chirurga* M. Oliverius (IKEM, Praha)
18.40-18.50	Echinococcosis: the invasive radiologist's view/*Echinokokóza z pohľadu invazívneho rádiológa* S. Okapec (FDR, Banská Bystrica)
18.50-19.00	**Discussion/*Diskusia***
19.00	**Welcome reception/*Uvítací večer***

Saturday/Sobota, 17 June 2017	
9.00-11.15	**III. Blok** Predsedníctvo: S. Fraňková, P. Kristián, M. Janičko
9.00-9.45	HIV, HBV, HCV: Slovak permutations/ *HIV, HBV, HCV: SK Permutácie* P. Jarčuška (UPJŠ, Košice)
9.45-10.00	HBV infection, ACLD and liver transplantation/ *HBV infekcia, ACLD a transplantácia pečene* S. Fraňková (IKEM, Praha)
10.00-10.15	Secondary hepatotropic viruses and ACLD/ *Sekundárne hepatotropné vírusy a ACLD* P. Kristián (UPJŠ, Košice)
10.15-10.30	Non-hepatotropic virus infections in ACLD/ *Nehepatotropné vírusové infekcie pri ACLD* E. Lovrantová (FDR, Banská Bystrica)
10.30-10.45	HAV in ACLD and after liver transplantation/ *HAV pri ACLD pečene a po transplantacii pečene* L. Paraličová, M. Novotný (UPJŠ, Košice)
10.45-11.15	Hepatitis E: review and situation on Slovakia/ *Hepatitída E: prehľad a situácia na Slovensku* I. Schréter (UPJŠ, Košice), S. Adamcová-Selčanová (FDR, Banská Bystrica)
11.15-11.30	**Coffee break**
11.30-12.40	**IV. Blok** Predsedníctvo: P. Trunečka, Š. Hrušovský, E. Lovrantová
11.30-11.45	Diagnosis of sepsis in the era of omics/ *Diagnostika sepsy v ére "omics" technologií* M. Průcha (Nemocnice Na Homolce, Praha)
11.45-11.55	Infection in the pathogenesis of portal hypertensive bleeding/ *Infekcie v patogenéze krvácania pri portálnej hypertenzii* J. Baláž, M. Brunčák (FDR, Banská Bystrica)
11.55-12.05	The allocation of antibiotic therapy by MIC and penetration: the use of software in ACLD/ *Alokácia antibiotickej liečby podľa MIC a penetrácie pri ACLD za pomoci softvéru* A. Purgelová (FDR, Banská Bystrica)
12.05-12.15	Infections after liver transplantation: Review/ *Infekcie po transplantácii pečene: Review* P. Trunečka (IKEM, Praha)
12.15-12.25	The role of histopathologist in the diagnosis of patients infections after liver transplant patients/ *Úloha histopatológa pri diagnostike infekcií u pacientov po tronsplantácii pečene* E. Honsová (IKEM, Praha)
12.25-12.40	Vaccination in patients with ACLD, before and after liver transplantation/ *Vakcinácia u pacientov s ACLD, pred a po transplantácii pečene* L. Krištůfková (FVZ – SZU, Bratislava)
12.40-12.55	**Coffee break**
12.55-13.50	**V. Blok** Predsedníctvo: J. Martínek, S. Dražilová, T. Koller
12.55-13.05	Bacterial infections in ACLD: cohort analysis/ *Bakteriálne infekcie pri ACLD: Analýza súboru* N. Bystrianska (FDR, B. Bystrica)
13.05-13.20	Fungal infections after liver transplantation: cohort analysis/ *Mykotické infekcie po transplantácii pečene: analýza súboru* S. Adamcová-Selčanová (FDR, B. Bystrica)
13.20-13.30	Infections in primary sclerosing cholangitis (PSC): Review/ *Primárna sklerotizujúca cholangitída (PSC) a cholangitídy: Review* J. Martínek (IKEM, Praha)
13.30-13.40	Antibiotic's prevention before endoscopic interventions/ *Prevencia antibiotikami pred endoskopickými zákrokmi* S. Dražilová (NsP, Poprad)
13.40-13.50	CAID(S): ACLD as a severe immune deficit/ *CAID(S): ACLD ako závažný imunodeficit* K. Kropáčeková, L. Hochmuth (FDR, B. Bystrica)
13.50-14.00	Concluding remarks/ *Ukoncenie SPH-9 – záverečné slovo*[2] P. Jarčuška, Ľ. Skladaný
14.00-15.00	**Lunch at the castie courtyard/*Obed no nádvorí zámku***

[1]Since cirrhosis is an anatomical diagnosis requiring a liver biopsy, the term 'compensated advanced chrnic liver disease' (cACLO) has been suggested rather than cirrhosis (Liver International 2017; 37 (Suppl 1): 104-115)
[2]Vyhlásenie troch najlepších pôvodných prác lekarov do 35 rokov

Oral section

Treatment of HCV infection in patients with liver cirrhosis and after liver transplantation

Robert Flisiak

Department of Infectious Diseases and Hepatology,
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Development of pangenotypic, highly effective and safe IFN-free medications based on combinations of 2-3 direct acting antivirals changed the landscape of HCV treatment. Their combinations provided sustained virologic response (SVR) rates >90% irrespective of liver fibrosis, disease advancement and treatment history. Additionally, these new therapeutic options are safe and allow to shorten treatment to 8-12 weeks in majority patients. IFN-free regimens provided opportunity to cure patients which were previously not allowed for IFN based therapeutic options, such as cirrhotics and liver transplant recipients.

According to EASL recommendations (2016) there is no difference between management of patients with compensated liver cirrhosis (Child-Pugh class A) and patients without cirrhosis. Patients with decompensated cirrhosis (Child-Pugh B or C) and MELD < 18-20 can be treated prior to liver transplantation as soon as possible, but protease inhibitors should be avoided in patients classified as Child-Pugh B or C. Patients with MELD ≥ 18-20 should be transplanted first, without antiviral treatment and followed for possible HCV recurrence. All patients with post-transplant recurrence should be considered for therapy, which should be initiated as soon as possible but optimal after 3 months post-transplant.

According to the most recent (2017) recommendations of the Polish Group of Experts for HCV, patients with Child-Pugh class C should be primarily recognized as eligible for liver transplantation. Howevre in patients with the MELD ≤ 20 antiviral therapy can be considered before the liver transplantation to suppress viral load to undetectable levels at least a month prior transplantation to protect transplanted liver from the infection. In patients with MELD > 20 antiviral therapy should be preceded by the liver transplantation, which also applies to patients with too short expected waiting period to ensure effective suppression of HCV.

Analysis of available real world experience (RWE) data collected from 13858 patients infected with genotype 1 treated with LDV/SOF ± RBV demonstrated SVR rate of 94% in the whole population and 92% in cirrhotics. OPr ± D ± RBV treatment efficacy analysed in 4260 patients showed SVR rate of 97% irrespective of cirrhosis status. RWE data for other regimens in cirrhotics such as SOF + SMV demonstrated SVR < 90%. Efficacy of LDV/SOF ± RBV and OPr ± D ± RBV in liver transplant recipients exceeded 90% in several available RWE studies.

Real world experience with interferon-based and interferon-free antiviral therapies against hepatitis C virus in Hungary

Béla Hunyady, Michael Makara

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and University of Pécs, Pécs, Hungary
Saint Laslo and Sint Istvan Hospital, Budapest, Hungary

Between 2002 and 2015, approximately half of eligible hepatitis C (HCV) infected patients could be effectively treated with pegylated interferon (PegIFN) + ribavirin (RBV) dual therapy to reach a sustained viral response (SVR). The efficacy has been increased by adding direct acting antiviral drugs (DAA-s: boceprevir, telaprevir or simeprevir) to the PegIFV + RBV regimen in 2013 and 2014. However, IFN-related side effects as well as IFN contraindications have limited the efficacy and/or the applicability of these regimens. Due to financial constraint, the PegIFN + RBV combination is still in use in Hungary as mandatory first line therapy for patients with no contraindication. Data of 774 treatment-naive PegIFN + RBV treated patients starting treatment between 01 August 2013 to 31 July 2015 have been retrospectively collected from the Hungarian Hepatitis Registry. Since genotyping (GT) is not mandatory for IFN-based therapy in Hungary, GT distribution is unknown (however, appr. 90% GT1b based on epidemiology data). Fibrosis staging (FS, also not mandatory) is available for 63% of patients: liver stiffness (LS) < 9.6 kPa in 36%, ≥ 9.6 kPa in 27%, unknown in 37%. An unsatisfactory 35% total SVR rate is predicted (42% – 27% – 37%, according to FS/LS categories mentioned) – although patients with more advanced cirrhosis (decompensated or LS > 20 kPa), or with other negative predictors (HIV co-infection, post liver/organ transplant, relevant baseline cytopenia, specific other co-morbidities) have not been treated with this regimen in Hungary during this period of time.

Since 2015, HCV infection (especially genotype 1b, most frequent in Hungary) can be cured with combination of different DAAs (± RBV), without use of IFN, providing an SVR rate of > 95% in almost all patient populations in need. Since May 2015, two of these regimens (ABT3D ±

RBV = ritonavir boosted paritaprevir/ombitasvir ± dasabuvir ± RBV or LED/SOF ± RBV = ledipasvir/sofosbuvir ± RBV) have been available in Hungary, too, for a proportion of patients (based on a severity/urgency-driven priority system). With unfortunately > 1500 diagnosed and eligible patients still on a waiting list for these therapies, 912 patients (GT1b = 89.7%; FS < 4: 18%, FS = 4: 60%, FS not known: 12%; ABT3D ± RBV, *n*: 664, LED/SOF ± RBV, *n*: 248) have been treated by December 2016 in Hungary with an overall SVR rate of 97% (ABT3D ± RBV: 98.5%, LED/SOF ± RBV: 93.1%). Patients treated with LED/SOF ± RBV had higher average LS (32.9 kPa vs. 25.1 kPa), and included 114 patients (46%) with Child-Pugh B or C stage cirrhosis.

In conclusion, IFN-based therapies are significantly underperforming (SVR < 40% in real world experience) and raise safety and/or adherence issues in a large proportion of patients compared to IFN-free therapies (SVR > 95%). For this reason, IFN-based therapies should not be used for the treatment on any patient – regardless of potential (probably nor existing) financial reasons.

Role of serologic markers in the diagnosis and prognosis of bacterial infection in cirrhosis

Maria Papp

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Infectious episodes represent particularly important causes of progression of liver failure and the development of liver-related complications. In cirrhosis, accurate prediction, early recognition and prognostication of bacterial infections are equally essential to surmount complications, delay progression and diminish mortality, however these are challenging in the clinical practice. Serologic markers related to these processes can assist clinicians in decision-making when establish treatment and care strategy for the patients suffering with end-stage liver disease.

Pathological bacterial translocation (BT) is increamentally increasing with diseases severity in cirrhosis and has an important role in the development of systemic infections. Inflammatory state sustained by BT is sufficient alone to elevate inflammatory markers to a significant level, even in the absence of without presence of overt infection. Accordingly, of the acute phase proteins (APPs) namely low-grade increases in the level of C-reactive protein (CRP) and lipopolysaccharide binding protein (LBP) were established as risk factors for developing of systemic bacterial infections. Recently, IgA isotype of various serological antibodies directed against gut innate immune proteins or intestinal microorganisms have also been reported as reliable markers of infectious risk in this patient population. Presence of target specific IgA antibodies could be a clue of an excessive mucosal immune response due to extended microbial challenge or dysregulation thereof.

In the clinical practice, conventional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT), are used most frequently in the diagnosis of bacterial infection. However, several diseases specific pitfalls attenuate the diagnostic accuracy of these APPs in cirrhosis. Firstly, if the main source of the APP is the liver, synthesis of protein can be affected by liver failure and its severity. Secondly, depending on molecular weight renal failure and also renal replacement therapy can be confounding factors. Acute kidney injury is frequent in patients with cirrhosis, especially in bacterial infections. Novel markers, such as presepsin or mid-regional pro-adrenomedullin (MR-proADM) have also some drawbacks. Excessive elevation in the level of certain APPs, particularly PCT or anti-inflammatory response related molecules (soluble[s] CD163, soluble urokinase-type plasminogen activator receptor [suPAR], monocyte HLA-DR loss or sTNF-R) are associated with higher risk of short-term mortality during bacterial infections and supposedly represent the deleterious effect of the exaggerated inflammatory processes.

Conclusions: Novel biomarkers being devoid of the limitations of classic APPs are highly needed to optimize the rule in and rule out processes necessary for the diagnosis and also for the severity assessment of bacterial infections. Furthermore they may help the identification of patients at high risk for developing systemic infections and those that mostly have advantage from prophylactic measures.

Direct acting antivirals (DAA), hepatocellular carcinoma and HBV reactivation: Controversies

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Direct acting antivirals (DAA) combinations have an excellent efficacy and tolerability in contrast to the interferon-based regimens in the treatment of chronic hepatitis C (HCV). However, DAAs have no immunomodulatory effect and the elimination of HCV provides a shift in immunological control in the liver. A decrease in interferon-stimulated genes expression and NK-cells function normalisation in the liver was described by Serti *et al.*

Furthermore, Vilani *et al*. described an increase of vascular endothelial growth factor serum levels accompanied by the decrease in IL-10 and TNF-α levels. The changes in immunological parameters represent the molecular basis for other viruses resurgence and uncontrolled growth of HCC.

In HCV/HBV coinfection, HBV DNA level is often low or undetectable and HCV is usually the main driver of chronic hepatitis activity. HBV may reactivate after HCV eradication. HBV reactivation was described across various DAA regimens, i.e. simeprevir + sofosbuvir (± ribavirin) or ledipasvir/sofosbuvir. 29 cases of HBV reactivation in time relation to DAA initiation were recorded in the FDA database from 11/2013 to 10/2016. Reactivation typically occurred within 4-8 weeks of HCV therapy initiation, and most patients were from Japan (66%) and the rest form the US or other countries (17% each). In these 29 cases, 2 patients died, 1 got liver transplantation, 6 were hospitalized, and 10 discontinued DAAs. Consistently with the above-described, the latest EASL guidance (2016) recommended that these patients should be tested for HBsAg, anti-HBc and anti-HBs. Concomitant HBV therapy is indicated if HBsAg is present or if HBV DNA is detectable in HBsAg-negative, anti-HBc positive patients.

HCC occurs in 1-7% patients with cirrhosis per year. The risk correlates with fibrosis stage. SVR is associated with a reduced mortality and risk of HCC. Conti *et al*. followed-up 344 individuals with liver cirrhosis for 12-24 weeks after completion of DAA therapy, 59/344 patients had undergone a curative treatment of HCC before therapy. HCC incidence within 24-week period after DAA treatment was 7.6%, in those without HCC 3.2%. In the group with previous HCC, the recurrence rate was 29%. In contrast, in a French study evaluating retrospectively 6000 patients, an increase in HCC incidence after DAA treatment was not confirmed. The patients at risk of HCC should be carefully screened for HCC after DAA therapy by the means of ultrasound every six months.

Antimicrobial stewardship program (ASP) on hepatogastro-transplantation unit (HEGITO)

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Introduction: There are two methods of ASP: 1. Prior authorisation of certain restricted antimicrobials (atb)*. 2. Prospective audit and feedback**. The first aproach leads to reduction of restricted atb but increase use of non restricted drugs. Second aproach helps the physician to choose the most appropriate therapy and with prospective analysis identificate and eventually correct suboptimal management of infectious disease (ID). This method shows lower atb use, lower number of new atb prescriptions with improved physician satisfaction. The change-over from first to second aproach is multi-step process, which requires: 1. Collect data about every infectious event. 2. Identify most frequent ID in specific departements. 3. Prepare guidelines for their management. 4. Analyse collected data and find if there is right drug choice, right dose, culture directed de-escalation and right duration.

Aim: To introduce first experiences with transfer proces from the front-end* to the back-end** ASP aproach on HEGITO.

Method: Descriptive statistical analysis of the data (age, gender, reason of hospitalisation, diagnosis of the infectious disease, atb, effect of therapy) extracted automatically from atb indication questionnaire (IQ). IQ should be completed in hospital information system for any formaly restricted atb. Any IQ require prior authorisation by the member of hospital ASP committee. First atb dose was allowed. We analyse the IQs since 1.1.2015 to 31.12.2015. We were recording compliance of ID management with guidelines, finished after this time period, and identify the targets of future ASP intervention.

Results: We analysed 192 episodes of ID, in 133 pt., 65 man and 68 woman, with average age 53,5y (19.4y-84y). We have recorded 52 (27%) lower respiratory tract infections (RTI), 50 (26%) blood stream infection (BSI), 29 (15%) billiary tract infection (BTI), 26 (13.5%) spontaneous bacterial peritonitis (SBP), 23 (12%) urintary tract infection (UTI). Empirical atb choices were 47 (33%) chinolons, 39 (20%) piperaciln/tazobactam, 35 (18%) meropenem, 22 (11%) vancomicin, 10 (5%) amikacin, 5 (2.5%) cefoperazon/sulbactam, 5 (2.5%) linezolid. Successful empiric therapy was recorded in (72%) ep. Clincal or laboratory rezistance to empric therapy was in 21%. In hospital mortality on empiric treatement was 14%. Most frequent inhospital mortality was in upper UTI 25% and BSI 16%. Most frequent resistance to empiric atb terapy was in lower RTI 36% and in BTI 29%. Compliance with ASP guidelines:

ID drug dose deescalation duration
RTI 21% 100% 0% NO DATA
BTI 59% 100% 0% NO DATA
SBP 41% 100% 0% NO DATA
UTI 0% 100% 0% NO DATA

Conclusions: ASP on HEGITO demostrate:
1. High resitance to empiric atb choice.
2. Low compliance with subsequently developed guidelines.
3. Overuse of chinolons.

Targets for ASP intervention are to increase compliance with drug choice and deescalation.

Gut microbiota and ACLD

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Current scientific evidence supports that the gut microbiota plays a crucial role in human metabolic and immune homeostasis. As the microbial components and metabolites can cross the gut barrier and enter portal venous blood, the cells located in the liver are constantly exposed to gut-originated substances which interact with large specter of pattern recognition receptors (PRRs) and associated signaling molecules. Advancements in next-generation sequencing technologies during last several years enabled a thorough description of microbial composition in large cohorts of patients with both intestinal and/or extraintestinal diseases. Observed microbial alterations included various liver disorders such as alcoholic liver disease, non-alcoholic fatty liver disease and advanced cholestatic disorders. Several studies established that the liver cirrhosis is, among other distinct features, characterized by overrepresentation of oral microbes in lower levels of gastrointestinal tract.Recent study from Institute for Clinical and Experimental Medicine in Prague (IKEM) indicate that also primary sclerosing cholangitis (PSC) and concomitant inflammatory bowel disease (PSC-IBD) are associated with disease-specific dysbiotic features. These included changes in global microbiota composition, disturbance of gut microbial diversity and altered abundance of specific bacterial taxa.

Revealing the specific features of liver disease-associated dysbiosis might contribute to establishing suitable biomarkers predicting the clinical course of advanced chronic liver diseases. Furthermore, deeper understanding of host-microbiota interactions regarding specific microbial taxa might set path towards novel therapeutic targets.

Management of hepatic abscess

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Hepatic abscess (HA) remains a serious and often difficult to diagnose problem, because of the nonspecific symptoms and laboratory findings. HAs can be divided into three main categories based on the underlying conditions: infectious, malignant, and iatrogenic. Infectious abscesses include those secondary to direct extension from local infection, systemic bacteremia and intra-abdominal infections that seed the portal system. However, over the years, the etiologies and risks factors for HA have continued to evolve. Pyogenic HA are relatively rare, though untreated are uniformly fatal. A recent shift in the management of liver abscesses, facilitated by advances in diagnostic and interventional radiology, coupled with improvements in microbiological identification and therapy, have decreased mortality rates to < 5-30%. Depending on its characteristics, HA can be effectively treated by either percutaneous or surgical drainage in combination with antibiotics. Early recognition of HA is important for instituting effective management and achieving good outcomes.

Echinococcosis: the infectologist's view

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Echinococcosis is a disease caused by the larval stage of tapeworm from genus *Echinococcus*. Humans become accidental intermediate hosts. There are two types of echinococcosis – cystic (CE), which is caused by *E. granulosus*, and alveolar (AE) caused by *E. multilocularis*. Slovakia is an endemic region of both species. The final host of *E. granulosus* is a dog for *E. multilocularis* it is a fox. After ingestion of eggs by intermediate host the released larvae migrate to organs, usually to the liver, where they produce cysts. Cysts caused by *E. granulosus* are marginated, coated with rigid fibrous membrane. They produce daughter cysts inside the cyst and eventually they calcify. However, they may rupture, what can lead to a severe allergic reaction and hematogenous seeding. Alveolar cysts are of malignant nature. They are made up of multiple separate vesicles and they are not bounded by fibrous membrane. They grow into the surrounding tissues and form new metastatic cysts in distant organs. Portal hypertension is a rare complication of echinococcosis. Portal hypertension caused by echinococci may be an intrahepatic (in AE), pre-hepatic and post-hepatic (more often with CE). Diagnosis of echinococcosis is based on imaging studies and the serological detection of antibodies. Currently, ELISA assays are the most commonly used. The sensitivity and specificity of individual tests vary greatly and not all commercially available tests are type specific. In practice, we have experience with delayed diagnosis of echinococcosis, often after surgery intervention for a "tumor", without previous serologic testing. Timely and correct diagnosis is essential for the optimal treatment. Better interdisciplinary cooperation is essential.

Echinococcosis: the invasive radiologist's view

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Hydatid disease is caused by the larval stages of *Echinococcus granulosus*. Most patients with hydatid disease have no symptoms, unless there is compression of vital organs such as the hepatic veins, portal vein, hepatic artery in the liver, resulting in life threatening complications. There are four treatment strategies for cystic echinococcosis (CE) – surgery, percutaneous methods, medical treatments and watch and wait strategies. Medical treatment with albendazol or mebendazole may cure only 2/3 of patients with CE. More than 30% of patients will reoccur after stopping the treatment. Watch and wait strategy is followed for asymptomatic and small cysts or CE type 4 and type 5 cysts. For the past two decades, invasive surgery was the recommended standard of practice for the treatment of CE. Today, only complicated cysts, such as biliary fistulae, ruptures in the peritoneum, invasion of the pleural cavity or bleeding into the cyst are surgically treated. Radical and conservative surgical techniques have a higher mortality (2-4%) and morbidity (11-23%) rate, with greater recurrence (2-10.4%) of re-infection and a longer rate of hospitalization than in PAIR (puncture, aspiration, injection, re-aspiration) and Örmeci technique. Both the PAIR and Örmeci techniques are safe and effective. However, the Örmeci technique offers a simpler, inexpensive method of treatment, with no mortality, lower morbidity, low recurrence rate. It can be used as the first choice of treatment modality in patients with cysts type CE type 1, CE type 2, CE type 3A and CE type 3B.

HBV infection, ACLD and liver transplantation

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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 have led to improved survival in HBV patients, reduced HCC incidence as well as improved survival after liver transplantation (LT). Although once considered a contraindication to LT, with introduction of nucleos(t)ide analogues (NUCs) in HBV therapies, LT represents now the crucial cure for HBV-related end-stage liver disease or HCC.

Decompensated HBV-related cirrhosis is an uncommon condition and the main indication for transplantation in HBV-infected patients will continue to be HCC. In decompensated HBV cirrhosis, the indication for LT is similar to other causes of cirrhosis. In addition, 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 o tenofovir should be started as soon as possible. The antiviral treatment has two objectives: 1) the improvement of liver function; and 2) to decrease the risk of HBV recurrence after LT since viral replication level at the time of LT correlates with the risk of HBV recurrence, positive HBV DNA at the time of LT seems to influence mortality due to HBV recurrence in HBV/HCC patients.

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 patients awaiting LT. 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 MELD score > 20, particularly when treated with entecavir. About one third of patients who initiate therapy have improvement in liver function, which in some cases might result in patient delisting. Cases of severe HBV reactivation should be considered specifically: the treatment with NUCs is an emergency.

After LT, lifelong prophylaxis of HBV recurrence in the liver graft based on either hepatitis B immune globulin and NUCs or NUCs alone is the gold standard.

Secondary hepatotropic viruses and ACLD

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In addition to the nominal hepatitis viruses (A to E), there are other viruses that can also cause liver inflammation including herpes virus family (EBV, CMV, HSV, VZV...), adenoviruses, rubella, morbilli, parotitis, coxackie and echoviruses. Majority of them causes primary infection in childhood or young age. Liver injury caused by these viruses is very common, usually only mild or mod-

erate and of short duration. Fulminant course of infection is possible, but extremely rare. They may not present in chronic form and cannot lead to liver cirrhosis.

Some of them, especially CMV, may pose a special risk to patients with chronic hepatitis or cirrhosis of another aetiology (e.g., also in immunocompromised patients). CMV infection represents one of the most frequent opportunistic infections following solid-organ transplantation including liver transplantation. Furthermore, an association between CMV positive donor and negative recipient serodiscordance and severe HCV recurrence in patients undergoing liver transplantation for HCV liver disease was described. Other observation suggests that CMV may represent an important factor for HCV response to interferon treatment in CMV/HCV coinfected patients.

Results of a large retrospective study indicate that CMV seroprevalence in patients with HCC is significantly higher than in patients without HCC, is positively correlated with serum IL-6 levels in cirrhotic patients, and is positively associated with the presence of other hepatotropic viruses such as HCV and HBV.

Most of these observations are supported only by a few data. Future studies will be needed to define the role of CMV in ACLD.

Nonhepatotropic viral infection in ACLD

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ACLD, which is associated with specific symptoms of the immune dysfunction, is the final stage of chronic liver diseases of various etiology. Both suppression and hyperergy, paradoxically make their concurrent appearance in the system resulting in the increased reactivity on the acute inflammation, which occurs either locally, or more distant.

The worst consequence seems to be a disbalance of proinflammatory and anti-inflammatory processes with a decompensation of ACLD and a development of ACLF. Although some of the triggers causing this decompensation are already identified, 20% to 40% remain to be still unknown. Etiopathogenesis of unexplained conditions may include influence and consequences of certain infections, also known as non-hepatotropic infections. In case of viral infections, we experience the so-called parainfectious hepatopathy or the exacerbation of the chronical, potentially hepatotropic infection occurring during a viral disease. It seems that the main role is played by the immunity system affected by an expansion of T-lymphocytes activated by an extrahepatic viral infection.

A good example might be a so-called "collateral damage", the model of an accompanying parallel liver damage caused by the influenza virus. The related clinical picture indicates several conditions – from a mild, nonspecific reactive hepatitis, through focal inflammatory processes and fulminant, seronegative hepatitides, to rare fatal form of hepatitis. At the same time, the influenza virus itself has not been identified in the liver. Evidence proves that the influenza virus may cause an exacerbation of the chronical liver disease and can further trigger a rejection of the transplanted liver.The overview of several other viruses that may cause a parallel liver damage is included in the presentation.

A bacterial superinfection of respiratory viral infection is also a complication, which is far from being insignificant. This fact is not only another reason for an early diagnosis and treatment but also justifies further prevention (i.e. vaccination), which respects concurrent viral diseases of patients with ACLD. An early intervention may reduce morbidity and mortality of affected patients and, on the other hand, may positively influence savings in the public health care sector.

Acute hepatitis A in patients with chronic liver disease

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Acute hepatitis A (HAV) has mainly an uncomplicated clinical course. In conditions of acute on chronic liver disease reports have indicated contradictory results. Superinfection with hepatitis A virus is generally held to cause acute hepatic failure and higher fatality rates in patients with underlying chronic liver disease, specifically chronic hepatitis B virus (HBV) infection, alcohol abusers but rarely with chronic hepatitis C virus (HCV) infection. There is also possible to find information about reduction or complete eradication of HCV replication in conditions of HAV superinfection in chronic HCV infection. We evaluated the clinical and virological characteristics of hepatitis A virus infection in conditions of chronic liver disease in patients hospitalized at the Department of Infectology and Travel Medicine in Košice. Fulminant HAV is an uncommon disease but according to evidence and our experience is there suspicion for higher incidence in condition of chronic liver disease.

Hepatitis E: overwiew and situation in Slovakia

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Hepatitis E virus (HEV) is the most commom cause of acute hepatitis in the developing countries with reduced sanitary conditions and occurs in both sporadic and epidemic forms. High attack rate is typical in young adults. Acute infections are very severe among pregnant women. In Europe for long time it was considered as imported, acute, self limited disease. From the year 2008 in Slovak republic (SR) 98 cases of acute hepatitis E were recognized. All cases except 14 had no traveler history. In our pilot study we found 43.5% (76 from 175) anti-HEV prevalence in general adult population. First evidence about infections among patients with chronic liver diseases are now also available from SR. From group of 589 patients with elevated aminotransferases 65 was positive for serologic markers of hepatitis E. Formerly it had been assumed that HEV is only the cause of acute hepatitis. Over the last few years HEV infection has been recognized as chronic hepatitis in immunocompromised persons (solid organ transplantant recipients, HIV-infected patients, patients with hematologic malignancies).

Diagnostics of sepsis in the era of "omics" technologies

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Option in understanding sepsis pathogenesis and thus in sepsis therapy is linked to the technologies enabling evaluation of gene expression and its regulatory mechanisms in addition to search for new proteins and metabolites produced in septic patients. Genomics, epigenetics, transcriptomics and metabolomics all represent such scientific quest.

Numerous studies have attempted to associate genetic markers of genomic variation (polymorphisms) with incidence or outcome of infectious disease and its sequelae in critically ill patients. TNF gene polymorphisms showed association with an increased incidence as well as adverse outcomes in patients with severe sepsis and septic shock (Stuber *et al.* 1996). Specific allelic variants of the TNF locus are associated with increased susceptibility and adverse outcome of sepsis. Candidate gene studies have been extended towards pro- and anti-inflammatory cytokines like the IL-1 gene family, IL-6 and IL-10 (Fang *et al.* 1999). Genomic variants of candidate genes involved in pathogen recognition and signal transduction of inflammatory pathways like CD14 and TLRs may also contribute to incidence, severity and mortality of infectious complications in the critically ill (Hubacek *et al.* 2001; Mansur *et al.* 2015). Latest findings from a European wide multicentre trial identified variants in the FER gene which are associated with a reduced risk of death from sepsis due to pneumonia (Rautanen *et al.* 2015). Genes activity varies due to different epigenetics mechanisms. The main principle is gene expression variability without the change in DNA sequence (Phillips 2008). The example of this phenomenon is the bacteria-host interaction. Bacterial-induced epigenetic deregulations may affect host cell function either to promote host defense or to allow pathogen persistence. Thus, pathogenic bacteria can be considered as potential epimutagens able to reshape the epigenome (Bierne *et al.* 2012). Transcriptomics evaluates messenger RNA levels for genes in specific cells or tissue. Transcriptomics is used in diagnosis of sepsis for discrimination between infectious and non-infectious inflammation (Prucha *et al.* 2004; Tang *et al.* 2010). It can also identify biomarkers for assessment of pathogenetic course and prognosis of the disease (Davenport *et al.* 2016). The main goal of proteomics is to identify proteins, biomarkers which are produced in septic patients and thus can help in accurate diagnosis of sepsis (Paugam-Burtz *et al.* 2010), or to detect proteins and to describe their function on the molecular level in sepsis (Buhimschi *et al.* 2011). The term metabolom includes intra and extracellular low molecule substances which are the product of metabolic pathways needed for cell growth and its function. Metabolomics is complete analysis of metabolom in given physiological or pathological state of the cell, tissue and organism and it provides new insight on cellular fiction (Goodacre *et al.* 2004). It can be used in septic patients for diagnosis, disease prognosis and for the patient's risk stratification (Ferrario *et al.* 2016; Kauppi *et al.* 2016).

Infections in the pathogenesis of bleeding in portal hypertension

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Infectious complications significantly increase mortality in patients with end-stage liver disease and are considered a major medical challenge. Higher incidence of systemic infections, deficiencies in immune system caused by liver dysfunction and bacterial translocation from digestive tract represent the main identified causes of infections in cirrhosis. The pathophysiological mechanisms initiated by infection lead to reduced intrahepatic vasodilatation and increased intrahepatic vasoconstriction, and hence result in increased risk of acute variceal bleeding. Identification of mechanisms and signal molecules involved in the process offers possibilities of new diagnostic and therapeutic approaches to portal hypertension.

Infections in liver transplant recipients: A review

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Infections are very important cause of morbidity and mortality of the host at all time periods after liver transplantation, being the most common complication with incidence rate 20-80%. They could be divided into 4 groups: 1) infections transmitted by donor organ, 2) infections associated with the surgery (= infections of early post-transplant period), 3) late opportunistic infections of immunocompromised host, 4) reinfections of HBV or HCV positive recipient.

Immunosuppressive therapy as well as advanced liver failure contribute to susceptibility of the recipient, most importantly to infections of the 2 group.

1) Most common infections transmitted by graft are bacterial and yeast infections. Multidrug resistant pathogens could be transmitted, esp. if donor was long-term hospitalized and ventilated, and could cause severe sepsis in recipient. Transmission of hepatitis B, C, and E viruses is limited by donor testing, but still possible. Transmission of parasites (*Strongyloides*, *Tripanosoma cruzi*) was described. Graft from donor tested positive for *Treponema pallidum* may be transplanted but recipient must be treated with Penicillin.
2) This type of infectious complications is caused mostly by Gram- bacteria (originated mostly from colonized host), or by nosocomial infection (often also Gram+). Multidrug resistant pathogens (MRSA, VRE, ESBL+) could cause serious problems. Most programs employ short-term ATB prophylaxis according to local practice, all cases of high risk recipients (acute liver failure, re-transplantation, high blood loss, patients with kidney failure, and reoperations should be covered by antifungal prophylaxis. All patients in early post operation period are protected by prophylactic treatment for *Pneumocystis,* occasionally for *Legionela pneumophilla*. CMV, *Tuberculosis,* and *Toxoplasma* require specific protocols of prophylaxis.
3) It is difficult to draw line between infections of early and late post-transplantation period, agents of group 2 could cause complications any time after transplant. The most typical opportunistic infections are caused by *Listeria*, *Nocardia*, herpetic viruses (CMV, EBV, HVV6, Varicella zoster virus). Especially serious are infections caused by *Cryptococcus*, *Mucormycosis*, and *Aspergillus*.
4) Hepatitis C recurrence could be challenging even in era of DAA if rare viral resistance is present. Post-transplant prophylaxis for HBV must be continuous.

In transplant candidates and recipients, proper vaccination is required. Live vaccines are contraindicated in most cases.

Infections after transplantation represents still major challenge and require fast and effective treatment measures in line with institutional guidelines for antimicrobial treatment and prophylaxis, that must be timely updated according to results of local microbial surveillance.

The role of histopathologist in the diagnosis of infections in patients after liver transplantation

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Despite advances in liver transplantation, morbidity and mortality due to infectious complications represent still serious problems. From the clinical point of view, it is useful to divide the post-transplant course into three time periods related to the risks of infection by specific pathogens: the early period post-transplant (first month), an intermediate period (1 to 6 months), and more than 6 months.

In the first month post-transplant, there are two major causes of infection in liver transplant recipient: infection derived from either the donor or recipient and infectious complications of the transplant surgery and hospitaliza-

tion. Donor-derived infections has increased with the emergence of antimicrobial resistance. Recurrent viral hepatitis may reemerge early after transplantation. Infectious complications related to surgery represent the common postoperative complications. Bacterial infections predominate; they usually have a nosocomial source.

In the period 1 to 6 months post-transplant, the patients are most at risk for the development of opportunistic infections, although residual problems from the perioperative period can persist. Viral pathogens, particularly the herpes group viruses but also de novo and/or recurrent hepatitis B and hepatitis C can occur. Two clinically and morphologically different types of B and C hepatitis are known, one with conventional morphology. The second, unique to the allograft termed fibrosing cholestatic hepatitis, with extensive hepatocellular damage and progressive development of liver failure. Recently, hepatitis E has been recognized more frequently as a cause of graft damage. Incidence and prevalence of hepatitis E post-transplant remains unclear but is certainly greater than historical estimates.

More than 6 to 12 months after transplantation, most patients are receiving stable and reduced levels of immunosuppression. These patients are subject to community-acquired pneumonias or severe illness from community-acquired infections. Recipients who have less than adequate graft function tend to require higher than usual immunosuppressive therapy. As a result, they represent a subgroup of transplant patients at highest risk for opportunistic infections typically encountered during the period of 1 to 6 months after transplant. They are also at risk for the late effects of viral infections manifest as malignancy: post-transplant lymphoproliferative disorder or squamous cell cancers of the skin or anogenital region.

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

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Introduction: Over the last 10 years, the overall mortality due to the consequences of liver cirrhosis (suggested to be called advanced chronic liver disease, ACLD) 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 (estimated at 1/3) affected by infections; the infections are the main reason for decompensation of ACLD (dACLD) on one hand and on the other they are a complication of dACLD, as well as the cause of death. The significance of infections in the outlook and pathogenesis is so great that "i" (infection) is added to the names of new syndromes (iACLF) or new definition of existing syndromes (iAKI).

Aim: Register and observational study HEGITO 7 to enable the evaluation of the association between infection and dACLD in the population of hospitalized patients at HEGITO.

Methods: Retrospective analysis of data in electronic database of NIS CareCenter Copyright 2000, CGM version 3.19.1 in patients with ACLD hospitalized at HEGITO BB between July 2014 and December 2015. Inclusion criteria: 1. ACLD; 2. Hospitalization at HEGITO; 3. Informed consent. Exclusion criteria: 1. Malignancy; 2. ACLD following orthotopic liver transplant (OLTx); 3. FMODA (Frequent low-volume ascites drainage through implanted peritoneal catheter); 4. Insufficient data Observed variables: gender, age, etiology of ACLD, Child-Pugh score (CPS), MELD (Model for End Stage Liver disease), type of infection in ALCD, mortality.

Results: The study population included a total of 235 observed patients (pts); inclusion criteria were satisfied by 217 pts (92.3%); 67 pts (30.9%) had a confirmed infection complication, in the remaining 150 pts (69.1%) no infection was diagnosed. In the population of patients with infection, there were 42 males (62.7%); with mean age of 54.3 years; 25 females (37.3%) with average age of 57.3 years. The observed population of patients with infection was dominated by etiological factor ALD (alcohol liver disease) 42 pts (62.7%); Child-Pugh score (CPS) was 10.34 ± 1.77 points; MELD score 18.46 ± 8.44 points. In the observed population of patients with infection, 25.3% pts had chronic decompensation (CD), 38.8% pts had acute decompensation (AD) and 73.3% pts had acute-on-chronic liver failure (ACLF). The occurrence of infections was as follows: with CD – prevailing infections of urinary system (35.7%), in AD group – spontaneous bacterial peritonitis (SBP) (19.4%) and in the ACLF group – sepsis (26.7%). In the population of patients with infection, the mortality during hospitalization was 14.9% (10 pts); while in the population of patients without infection, the mortality was 1.3% (2 pts) ($p = 0.001$).

Conclusions: Microbial infections represent a major problem in patients with ACLD. In the analyzed population of ACLD patients, we confirmed 30% prevalence of infections .The analysis failed to confirm the effect of gender, age and etiology on the development of infection

complications in the observed population of patients (p = NS), just the opposite – statistically significant association (p = 0.0001) was confirmed with respect to CPS and MELD. The greatest occurrence of infections was observed in the subgroup of patients with ACLE, as confirmed by the available publications where the bacterial infections are considered the most common initiating factor.The analysis also demonstrated a significant association between the infections and mortality, underlining their importance in this respect.

Fungal infection after liver transplantation: cohort analysis

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Introduction: Solid organ transplant (SOT) recipients have a significantly increased risk of fungal infections (FI). They are caused mainly by *Candida* spp., to a lesser extent by *Aspergillus* spp. During the past decade, non-albicans spp., like *C. glabrata*, emerged as an increasingly important causes of FI. Standard protocol of FI prophylaxis after liver transplantation (LTx) with fluconazole (FLU) has been declared ineffective. Careful examination of risk factors, diligent surveillance for early signs of infection, and prompt intervention are the mainstays of FI prevention. Due to the paucity of clinical trials there are no definitive recommendations on the diagnosis, treatment and prevention of FIs in SOT.

Aims: To determine 1) the prevalence of FI; 2) type of FI; 3) efficacy of FLU prophylaxis; 4) sensitivity to other antifungals; 5) lenght of hospital stay (LOS) 6) in hospital mortality (IHM) in LTx patients (pts) Transplant Center (TC) BB.

Methods: Retrospective analysis. The search of the Hospital Information System "Care Center®" and the database of the Department of Microbiology for the data of consecutive pts with LTx. Susceptibility testing was performed for FLU, itraconazole (ITR), voriconazole (VOR), other azoles and echinocandins. Study interval: May 2008 – January 2017. Inclusion criterion: LTx in TC BB. Exclusion criterion: LTx in other TC. Recorded variables: age, gender, agents of FI, sensitivity to FLU and other antifungals, MELD, LOS, IHM.

Results: During study interval 166 pts were enrolled, 95 men (57%), median age 55 years (17-76). FI was recorded in 116 pts (69%), in 155 cases. *Candida* spp. was present in 152 cases (98%), *Aspergilus* spp. in remaining 3 (2%). From all FI, *Albicans* spp. were identified in 91 (60%), 61 (40%) – non-albicans. The most common spp. was *C. albicans* – 91 (59%), followed by *C. glabrata* – 34 (22%), *C. krusei* – 9 (6%), *C. kefyr* – 5 (3%), *C. parapsilosis* – 5 (3%), *C. tropicalis* – 4 (3%), *C. lusitaniae* – 4 (2%) and *Aspergillus* – 3 (2%).

C. albicans was sensitive to FLU in 85 cases (95%), resistant in 5%; *C. glabrata* was sensitive to FLU in 24%, VOR – 98%, ITR – 1.85%, echinocandis – 100%; *C. krusei* was resitant to FLU in 100%, sensitive to VOR – 92.8%, ITR – 35.7%, echinocandins – 100%; *C. parapsilosis* was sensitive to FLU in 40%, other *Candida* spp. were sensitive to FLU, VOR and echinocandins in 100%. Median LOS in pts with FI was 34 days (d) (0-192), IHM – 11 (9%) and MELD (Model for End Stage Liver Disease) – 17.7 (9-33). Median LOS in pts without FI – 26.5 d (0-90), IHM – 2 (4%), MELD – 16.7 (8-43).

Conclusions: FI due to yeast are the most common infections after SOT. *Candida* spp. was the most common FI in pts after LTx at TC BB. The prophylaxis with FLU is effective in *Albicans* spp.; in non-albicans spp., the sensitivity is suboptimal. In pts with FI the LOS and IHM was higher. The incidence of FI in our cohort was indepentend of MELD score. Adequate prophylactic strategies with echinocandins can decrease the risk of FI.

CAIDS – ACLD as a severe immunodeficiency

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Liver as a primary immunological organ contributes the functioning of the immune processes through its "immunosurveillance" role and through the synthesis of proteins mediating immune reactions.

Thus every liver damage leads to immune dysfunction. This recent syndrome known as CAIDS (cirrhosis associated immune dysfunction syndrome) is a major factor in pathogenesis of the infectious complications in ACLD.

CAIDS is a severe dysfunction of both innate and adaptive immunity and a dysregulation in proinflammatory and counterinflammatory reactions. The CAIDS phenotypes vary from mainly proinflammatory state (exposition to DAMPs from damaged hepatocytes and PAMPs from increased bacterial translocation) through immunodefi-

ciency state to the exhaustion of the immune system, immune paralysis and indolent dead.

The immunomodulatory therapy possibilities are not well known yet and offers large field for the future study.

Our project is observing the possible effect of transfer factor (TF) on the incidence of infections and mortality in patients with ACLF (acute on chronic liver failure). It is a retrospective, case-control (propensity matched) study.

Poster section

Liver abscesses – an increasing problem (analysis of Derer's University Hospital in Bratislava)

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Introduction: The incidence of liver abscesses (LA) has been still rising over the past years. According to the etiology, bacterial (pyogenic), parasitic and mycotic abscesses may occur. Pyogenic liver abscesses are uncommon conditions that present diagnostic and therapeutic challenges to physicians. However, pyogenic abscesses (PA) are more common among patients at internal departments and mycotic are frequent in hemato-oncological patients.

Aim: To analyse the occurrence of liver abscesses in inpatients at 3rd Department of Internal Medicine and Department of Infectology and Geographical Medicine over the period of 5 years. Etiology, microbial origin, localization, type, length and outcome of the treatment were assessed.

Results: Pyogenic abscess was present in 11 patients. The mean age of patients was 57 years. The ratio of solitary to multiple abscesses was 6 : 5. The right localization (72.7% patients) was more common in comparison to the left (18.2%) or both lobes (9.1 %). In 4 patients (36.4%), there was biliary etiology and in 1 patient secondary infection of HCC (hepatocellular carcinoma) was present. Etiology of 6 patients remained unexplained. The most common microbial agent was Klebsiella pneumoniae. Positive blood or abscess´s cultivation was present in 6 patients (54.5%). Fever, nausea, vomiting and abdominal pain were most common clinical presentations. Inflammatory process was detected by laboratory findings, and imaging methods were helpful in detecting of their localization. All patients were treated with a parenteral combination of at least 2 types of antibiotics in the period of 6-9 weeks. Percutaneous drainage (PD) was made in 2 patients, repeated unsuccessful effort of PD was made in 1 patient, 6 patients did not need PD. 2 patients needed a surgical approach. In 3 patients death occurred due to sepsis and multiple organ failure. Remaining 8 patients were successfully treated. Clinical symptomatology disappeared by 8 weeks and PA disappeared by 4-6 months from the start of the treatment.

Discussion: Diagnosis of LA is not easy. The clinical presentation is not specific. Establishment of the diagnosis, from the onset of first symptoms, may vary from 2 weeks to 6 months. Fluidothorax or positive auscultation findings are common signs. The etiology of abscess (biliary disease, bacteremia, abdominal inflammation) may be present in a clinical picture. Laboratory findings together with clinical findings are crucial for detection of a serious infection and start of an antibiotic treatment. Imaging methods are key to localize of LA. A correlation of clinical and laboratory findings with an adequate sequence of imaging modalities is important in a clinical assessment. Early start of antibiotic treatment with PD may cure the patient.

Conclusions: Nowadays, liver abscesses are an increasing problem with multifactorial etiology and difficult diagnosis and treatment. The treatment has become more effective with a decrease in mortality over the last years. The possible causes of failure of a treatment involve mainly an increase of antibiotic resistance. Patient's management should be done in cooperation with the internist, infectologist, surgeon, and radiologist.

Acute-over-chronic liver failure (ACLF) in 305 HEGITO inpatients

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Introduction: ACLF – the new syndrome distinct from both chronic (CD), and acute liver failures. According to the landmark CANONIC study, ACLF is defined by baseline advanced chronic liver disease (ACLD), precipitating insult, acute decompensation (decompensating event present < 2-4 weeks), and is characterized by high short-term (28-day) mortality. It is associated with infec-

tions in around 30% of patients (i-ACLF), whereby iACLF has higher in-hospital mortality.

Aim: To determine the prevalence and the main characteristics of ACLF in patients admitted with decompensated ACLD, with special accent on iACLF.

Material and methods: Retrospective analysis (DJ). Consecutive inpatients. Inclusion criteria: admission to HEGITO with dACLD. Exclusion criteria: malignancy; insufficient data. Recorded variables: Age; gender; etiology of dACLD; type of dACLD: AD (ACLF 0-3 at admission and at day 7), CD; iACLF at admission; in-hospital mortality.

Results: During the period 7/2014 – 04/2016, 305 patients with dACLD were enrolled, 12 (4%) excluded, 215 with CD (70%), 78 with AD (26%). Median age was 56 years; female were 35n (45%); etiology with alcoholic liver disease (ALD) 65 (83%), autoimmune syndromes 11 (14%),other 2(3%). Decompensating events: ascites 55%, upper-GI bleeding 29%, hepatic encephalopathy 8%, infections 8%. Insults: acute alcoholic hepatitis 37%, GI bleeding 27%, bacterial infections 24%, unknown 9%, TIPS 3%. ACLF 1-3 was present in 35% (1 – 17%, 2 – 14%, 3 – 7%); iACLF – 24% of AD patients (SBP – 37%, respiratory – 21%, UTI – 15%, others-upt to 100%). Mortality in the AD group was 12%, as compared to 5% in CD group. Mortality in ACLF grades 1-3 was 18%, 50%, and 80%, respectively.

Conclusions: Prevalence of AD in patients hospitalized with dACLD was 26%, ACLF 1-3 was present in 35% of them. Mortality according to ACLF grades correlated with the data from literature. Infections played important role either as the insult, or event; small number of patients with iACLF precluded deeper analysis. Prospective collection of data is underway.

Bacterial infections and hepatic encefalopathy

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Introduction: Bacterial infections are common complication of patients with liver cirrhosis. Moreover, bacterial infections are frequent precipitating factor of hepatic encefalopathy. Infections are asociated with hepatic encefalopathy in 35% - 47% cases and getting worse prognosis of patient with liver cirrhosis.

Aim: Find out incidence of bacterial infections and asociation with hepatic encefalopathy in patients with ACLD.

Material and methods: Retrospective analysis from Hospital information system CareCenter Copyright 2000, CGM verzia 3.19.1 in patient with ACLD hospitalised on department HEGITO since 7/2014 until 12/2015. Inclusion criteria: 1. ACLD; 2. Hospitalisation on department HEGITO; 3. Informed consent. Exclusion criteria: 1. Malignancy; 2. ACLD after oLTx; 3. FMODA (Frequent small volume paracentesis via CAPD catheter); 4. Lack of information. Monitored variables: gender, age, etiology of ACLD, Child-Pugh score, MELD, hepatic encefalopathy, type of infection.

Results: Inclusion criteria fullfiled 235 patiens (pts), 18 pts were excluded, into defenitive analysis were included 217 pts. 67 pts (30.9%) had infectious complication, 150 pts (69.1%) were without infection. In the group pts with infection were 42 men (62.7%); with avarage age 54.3 years, 25 women (37.3%) with avarage age 57.3 years, the most common reason of cirrhosis was Alcohol liver disease (ALD) in 42 pts (62.7%), avarage Child-Pugh score was 10.34 ± 1.77 and avarage MELD 18.46 ± 8.44. In 32 pts with infection (47.76%) was diagnosed overt hepatic encefalopathy. The most common precipitating factor of hepatic encefalopathy were uroinfections (32.4%), SBP (21.6%) and infections of respiratory tract (16.2%).

Conclusions: One of the most common precipitating factor of hepatic encefalopathy are infections. In our retrospective analysis we finded out, that 48% pts with liver cirhosis and bacterial infection had also overt hepatic encefalopathy. The most common precipitating factor of hepatic encefalopathy were uroinfections, SBP and infections of respiratory tract.

Role of inflammasomes in liver diseases

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Introduction: A new term 'inflammasomes' has appeared in the literature over the last years.

Aim: Clarification of clinical significance of inflammasomes in chronic liver diseases.

Material and methods: Analysis of the review of the literature on this topic in the last eight years.

Results: Inflammasomes are molecular platforms activated upon cellular infection or stress that trigger the maturation of proinflammatory cytokines such as inter-

leukin-1b to engage innate immune defenses. They are multiprotein complexes responding to pathogen-associated molecular patterns (PAMP) and causing damage to them (DAMP-damage associated molecular patterns) and activate the inflammatory process. Various pathogens (toxins, alcohol, fat, viruses, etc.) may be activators of inflammasomes, most common due to alterations in the gut microbiota or increased intestinal permeability through toll-like receptors (TLR). Inflammasomes are regulators of inflammation and cell death. They are expressed and likely functionally active in the liver in hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells and macrophages.

PAMPs are mostly derived from the gut, due to alterations in gut microbiota composition and/or increased intestinal permeability. DAMPs are mostly derived from damaged hepatocytes and include ATP, uric acid, cholesterol crystals, DNA fragments, and fatty acids. The inflammasome can be activated either directly in hepatic stellate cells, Kupffer cells, and hepatocytes, or indirectly through cell death and increased exposure to PAMPs. Two steps are involved in inflammasome activation. The first step is signalization through TLR in bowel or IL-1 receptor with the following expression of inflammasome patterns. The second step includes releasing of caspase-1 with cytokine activation and secretion. Activation of inflammasomes culminates in caspase-1 activation and IL-1β secretion. IL-1 production has an auto-regulatory loop. The secreted active IL-1β or IL-1α can activate the IL-1 receptor complex and increase the transcription of its own precursor as well as the synthesis of the inflammasome components. This amplification loop suggests that small amounts of IL-1β could have a significant biological effect. In addition to inflammation, inflammasome activation regulates cell death. NLRC4 (NOD-like receptors C4) and NAIP- receptors activate pyroptosis, while NLRP3 (NOD-like receptors P3) activation contributes to pyronecrosis. Pyroptosis is a caspase-1-dependent cell death showing similarities to apoptosis and DNA damage. Unlike apoptosis, pyroptosis does not depend on apoptotic caspases, and it is accompanied by a loss of plasma membrane integrity and lack of chromatin condensation. Pyronecrosis shows similarities to necrosis since it is not caspase-dependent and leads to the breakdown of the plasma membrane without chromatin condensation.

There is increasing evidence that gut microbiota, increased gut permeability, and endotoxin contribute to the pathogenesis of both alcoholic (ASH) and non-alcoholic steatohepatitis (NASH). Endotoxin, a cell wall component of Gram-negative bacteria, is a major mediator of sepsis-induced liver damage, multiorgan failure, and chronic liver disease. Owing to the portal blood supply arriving from the intestines, the liver is exposed to high concentrations of nutrients and gut-derived substances including endotoxin. In ALD, serum levels of IL-1β are increased. Potential molecular triggers for inflammasome activation in NASH include DAMPs such as DNA, saturated fatty acids, and PAMPs. In primary hepatocytes, saturated, but not unsaturated fatty acids induce caspase-1 activation and IL-1β release in the presence of endotoxin. Danger signals from fatty acid-treated hepatocytes can induce inflammasome activation in liver mononuclear cells, suggesting a crosstalk between liver parenchymal cells and immune cells in NASH. This intercellular crosstalk provides potential amplification of inflammasome activation and inflammatory pathways in NASH. Fatty acid-induced inflammasome activation in macrophages is NLRP3-dependent and involved increased mitochondrial ROS production and decreased autophagy due to reduced AMPK activity. Chronic liver inflammation that is amplified by IL-1 leads to fibrosis and cirrhosis.

Conclusion: Inflammation is a common feature of chronic liver diseases (ALD, NAFLD, drug-induced liver injury), diabetes mellitus and atherosclerosis.

Inflammasomes and cytokines are the source of sterile inflammation in the liver resulting in fibrogenesis. Inflammasomes and IL-1 participate in all diseases with the autoinflammatory response and metabolic stress and may be related to complications. There is evidence that IL-1β, IL-18, and inflammasomes may also mediate encephalopathy. Caspase-1 and IL-18 levels are higher in patients with acute or acute-on-chronic liver failure compared to controls or patients with stable chronic liver diseases. Quite new therapeutic consequences are expected in the future on the basis of inflammasome inhibition and regulation of programmed cell death (necroptosis).

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