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# CROATIAN GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF PORTAL HYPERTENSION

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**SUMMARY** – Liver diseases are currently the eleventh leading cause of global mortality, and cirrhosis holds the ninth position among the causes of death in Europe. The progression of cirrhosis gives rise to complications such as portal hypertension (PH), liver failure, and development of hepatocellular carcinoma. PH plays a pivotal role in the advancement of chronic liver disease and stands as an independent predictor of mortality in individuals with cirrhosis. Given the numerous updates in the classification, diagnosis, and treatment strategies for PH, the adoption of national guidelines has become imperative to enhance the care of this patient population. In the wake of Baveno VII consensus, as well as the recently published data, the working group of the Croatian Society of Gastroenterology drafted the guidelines that were discussed and agreed during 2023. Herein, we present a condensed version highlighting the key recommendations.

**Key words:** *Portal hypertension; Vascular liver diseases; Guidelines; Diagnosis; Treatment*

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## 1 INTRODUCTION

Liver diseases are currently the eleventh leading cause of global mortality, resulting in around 2 million deaths annually and representing 4% of total deaths globally<sup>1</sup>. Cirrhosis holds the ninth position among the causes of death in Europe. Recent global trends indicate an upward trajectory in liver disease-related fatalities, with a notable increase anticipated, primarily driven by the rising incidence of metabolic dysfunction-associated steatotic liver disease (MASLD)<sup>2</sup>. The prevalence of excessive alcohol consumption, particularly notable in Europe, along with the ongoing challenge of chronic viral hepatitis, also contribute significantly to this evolving trend. The objectives outlined by the World Health Organization to achieve an 80% reduction in the incidence of viral hepatitis and a 65% decrease in mortality by 2030 are unlikely to be met. The progression of cirrhosis gives rise to complications such as portal hypertension (PH), liver failure, and development of hepatocellular carcinoma (HCC). Approximately 80%-90% of patients with compensated cirrhosis exhibit PH, with 60% experiencing clinically significant portal hypertension (CSPH) and 40% developing esophageal varices (EV)<sup>3</sup>. PH plays a pivotal role in the advancement of chronic liver disease and stands as an independent predictor of mortality in individuals with cirrhosis<sup>4</sup>. Given the numerous updates in the classification, diagnosis, and treatment strategies for PH, the adoption of national guidelines has become imperative to enhance the care of this patient population. The Croatian Society of Gastroenterology (CSG) initiated drafting of the national guidelines in 2022, forming a working group that presented a draft at the CSG annual meeting in Osijek on October 23, 2022. These guidelines were finalized in 2023, with the complete document in Croatian language published in the Croatian Gastroenterology Proceedings, the official journal of CSG in December 2023. Herein, we present a condensed version highlighting the key recommendations.

## 2 GENERAL ISSUES

### 2.1 Measurement and Clinical Significance of Portal Pressure

Measurement of the hepatic venous pressure gradient (HVPG) represents the gold standard for quantifying the severity of PH. In individuals with

viral hepatitis and alcoholic liver disease, an HVPG greater than 10 mm Hg serves as the criterion for identifying clinically significant portal hypertension (CSPH)<sup>5,6</sup>. CSPH is associated with an increased risk of developing varices, clinical decompensation and HCC<sup>5</sup>. HVPG values reflect sinusoidal PH and therefore may underestimate the presence and severity of PH in presinusoidal conditions and chronic liver diseases with both sinusoidal and presinusoidal components (such as primary biliary cholangitis and MASLD). In these conditions, decompensation may occur at the HVPG values below 10 mm Hg<sup>7</sup>. HVPG offers diagnostic and prognostic insights for individuals with cirrhosis, serving as a tool for evaluating the severity of liver disease, stratifying risks for complications, determining prognosis, and monitoring treatment responses<sup>8</sup>. HVPG  $\geq 10$  mm Hg is associated with an increased risk of decompensation after hepatic resection for HCC<sup>9</sup>. There is an elevated risk of esophageal bleeding when HVPG exceeds 12 mm Hg, and values surpassing 16 mm Hg indicate severe PH associated with treatment failure, early rebleeding, and mortality in variceal hemorrhage<sup>8,10</sup>. Values of HVPG  $\geq 16$  mm Hg are linked to a high risk of death after non-hepatic surgery<sup>11</sup>. Repeated HVPG measurements offer insights into the hemodynamic response to nonselective  $\beta$ -blocker (NSBB). Achieving NSBB-induced reductions in HVPG below 12 mm Hg or  $>10\%$  from baseline in primary prevention and 20% in secondary prevention markedly diminishes the risk of variceal bleeding, other decompensation events, and mortality<sup>12</sup>. Additionally, carvedilol demonstrates superior efficacy in reducing HVPG, correlating with lower rates of rebleeding, liver-related death, and nonbleeding decompensation in secondary prophylaxis of variceal bleeding compared to propranolol<sup>13</sup>.

### 2.2 The Concept of Compensated Advanced Chronic Liver Disease (cACLD)

Compensated advanced chronic liver disease (cACLD) indicates the presence of advanced fibrosis or cirrhosis in patients with chronic liver disease (CLD) without a history of decompensation, who are at risk of having or developing PH and its complications. This concept is based on the use of noninvasive diagnostic methods, primarily transient elastography (TE), which, on a continuous scale, stratifies the risk of PH complications. Liver stiffness measurements (LSM) play a crucial role in evaluating CLD severity. TE-

assessed LSM values below 10 kPa rule out cACLD, while a range of 10 to 15 kPa indicates a probable presence of cACLD, and values equal to or exceeding 15 kPa rule-in its presence. This diagnostic strategy facilitates the stratification of liver disease severity and informs on appropriate clinical management. The risk of decompensation over 2-5 years is minimal if LSM is below 10 kPa<sup>14,15</sup>, after which the relative risk of adverse outcomes increases for every 5 kPa<sup>16</sup>. Liver-related risk according to Fibroscan cut-offs differs also according to etiology, particularly between MASLD and ALD. For illustration, cumulative 5-year incidence of liver decompensation was 19.2% in ALD and 3.8% in MASLD, and was significantly influenced by baseline LSM, as demonstrated in a large multicenter study that evaluated natural history of 3,028 patients with cACLD as defined by the baseline LSM >10 kPa<sup>17</sup>. In patients with cACLD ( $\geq 15$  kPa), annual LSM monitoring is recommended due to increased (19%) risk of developing CSPH and

liver decompensation<sup>18</sup>. In clinical practice, the use of the 'rule of 5' for TE and 'rule of 4' for other shear wave elastography (SWE) methods is recommended, as different threshold values for TE (5, 10, 15, 20, and 25 kPa) and for other SWE methods (5, 9, 13, 17, 20-21 kPa) are employed to demonstrate a gradual increase in the risk of PH complications, decompensation, and mortality<sup>14,15</sup> (Fig. 1). The Baveno criteria for cACLD were validated in a multicenter study involving 5,648 patients who underwent liver biopsy and LSM by TE. It was found that the sensitivity of the Baveno criteria was suboptimal (75%), and new cut-off values were proposed: LSM <8 kPa for MASLD and ALD (<7 kPa for viral hepatitis), and >12 kPa, which had sensitivity and specificity >90% for ruling-out and ruling-in cACLD, and less patients were finally misclassified<sup>19</sup>. A reduction in LSM by >20% with LSM <20 kPa, or any decline in LSM to less than 10 kPa is associated with a reduction in the risk of liver decompensation and disease-related mortality<sup>20</sup>.

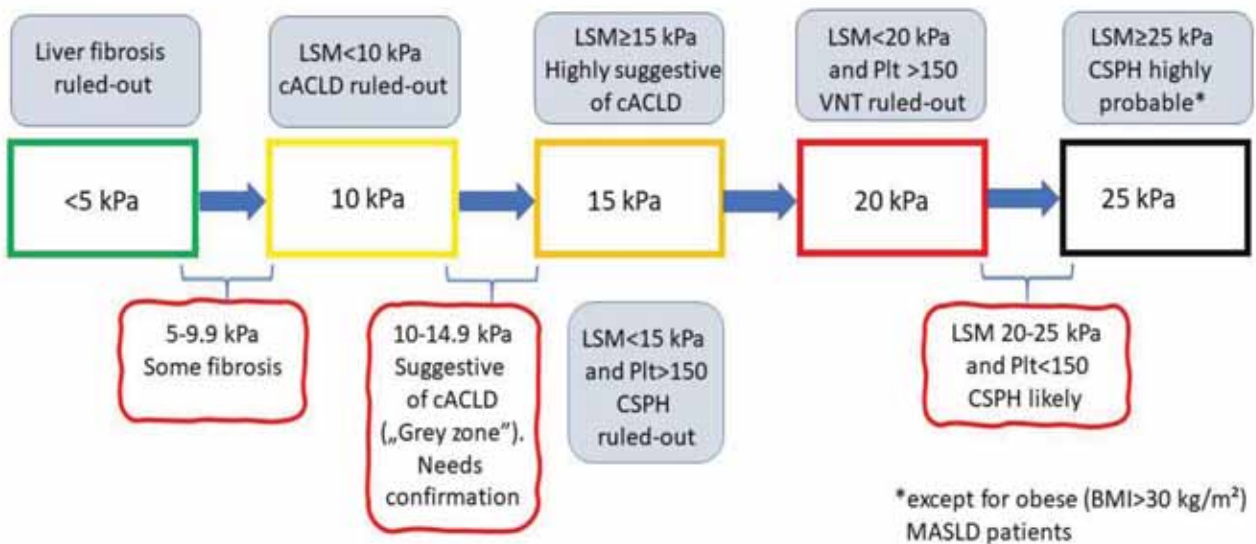


Fig. 1. Rule of five by transient elastography. Progressive increase in liver stiffness is associated with the increase of portal pressure (HVPG) and increased risk of portal hypertension-related complications and death.

VNT = varices needing treatment; MASLD = metabolic dysfunction-associated steatotic liver disease; cACLD = compensated advanced chronic liver disease; CSPH = clinically significant portal hypertension; BMI = body mass index; LSM = liver stiffness measurement; kPa = kilopascals; Plt = platelet count (Plt $\times 10^9/L$ ).

### 2.3 Noninvasive Diagnosis of Clinically Significant Portal Hypertension and High-risk Esophageal Varices

The criteria for noninvasive diagnosis of CSPH and high-risk esophageal varices (HRV) using TE and platelet count are provided in Table 1. Specific values and algorithms for ruling-in and ruling-out are presented for cACLD, CSPH, and HRV.

For LSM values in the range of 15–25 kPa, the so-called 'grey zone,' the LSM ANTICIPATE model can be used to predict the risk of CSPH<sup>6,22</sup>. Patients with decompensated cirrhosis, as well as those with varices or typical portosystemic collaterals by definition have CSPH. The best-evaluated among other elastographic methods is the two-dimensional SWE from the manufacturer Supersonic Imagine (Hologiq) (2DSWE.SSI). The threshold values of LSM are <13–14 kPa to exclude CSPH and >20–30 kPa to confirm CSPH<sup>23,24</sup>. Even when using SWE methods, platelet count should be considered as an additional criterion for excluding CSPH and HRV. For the 2DSWE

method from General Electric (2DSWE.GE), the published threshold values indicate that LSM <9 kPa rules-out CSPH, whereas LSM >13 kPa rules-in CSPH<sup>25</sup>. The published values for spleen stiffness measurements (SSM) using 2DSWE.SSI to rule-out CSPH range from 22–30 kPa, to rule-in CSPH around 35–40 kPa<sup>23,24</sup>, and to rule-out HRV <35 kPa<sup>24</sup>. For point shear wave elastography (pSWE) with virtual touch quantification (VTQ), the threshold values for SSM to rule-out CSPH and HRV are <2.5 m/s, and when LSM is >3.5 m/s, suspicion of esophageal varices arises. The published threshold values for SSM to rule-out HRV using the 2DSWE method from General Electric (2DSWE.GE) range from 11.5 to 17.9 kPa<sup>26</sup>.

### 2.4 Elimination of the Underlying Etiologic Factor

Elimination or suppression of the primary etiologic factor reduces HVPG and significantly decreases the risk of liver decompensation<sup>27</sup>. Notably, excessive body weight, diabetes, and alcohol consumption serve as

*Table 1. Criteria for noninvasive diagnosis of compensated advanced chronic liver disease (cACLD), clinically significant portal hypertension (CSPH) and high-risk esophageal varices (HRV) by using transient elastography (TE) and platelet count (Pltx10<sup>9</sup>/L)*

Condition	Rule-in	Rule-out	Notification
cACLD	LSM ≥15 kPa	LSM <10 kPa	LSM 10–15 kPa 'grey zone', another noninvasive test or liver biopsy is needed
CSPH	Baveno VII algorithm		*In obese patients (BMI >30 kg/m <sup>2</sup> ) with MASLD, LSM is unreliable.
	LSM ≥25 kPa* or SSM >50 kPa	LSM ≤15 kPa with Plt ≥150 or SSM ≤21 kPa	
	ANTICIPATE model (positive 2 out of 3 criteria)		**In obese patients, the specificity is less than 80%
	LSM ≥25 kPa, SSM >40 kPa, Plt <150**	LSM ≤15 kPa, Plt ≥150, SSM ≤21 kPa	
HRV	/	<20 kPa and Plt >150*** or SSM <40 kPa	***Probability of a false-negative result is <5%

MASLD = metabolic dysfunction associated steatotic liver disease; LSM = liver stiffness measurement; SSM = spleen stiffness measurement<sup>6,21</sup>



pivotal cofactors contributing to the progression of liver disease, persisting even after the resolution of the underlying liver disease cause<sup>20</sup>. Following successful eradication of HCV infection, patients manifesting reduced LSM values below 12 kPa and platelet counts exceeding  $150 \times 10^9/L$ , in the absence of contributing cofactors, may be exempted from further assessment for CSPH because the risk of developing CSPH and liver decompensation is negligible<sup>20</sup>. Nonetheless, the risk of HCC development persists, necessitating continuous monitoring. For individuals with viral hepatitis achieving virologic remission, the application of Baveno VI criteria (LSM <20 kPa + platelets >150) proves effective in excluding HRV<sup>28</sup>. In patients with cACLD on NSBB therapy and successful elimination of the etiologic factor accompanied by a reduction in LSM to <25 kPa, endoscopy should be repeated in 1-2 years. If varices are absent, NSBB therapy can be discontinued<sup>6</sup>.

## 2.5 Impact of Non-etiologic Therapy

Statins reduce portal pressure and systemic inflammation<sup>29</sup>. However, cautious approach is advised, particularly in Child-Pugh B and C cirrhosis, recommending lower doses (e.g., simvastatin 20 mg/day) with careful monitoring for rhabdomyolysis and hepatotoxicity<sup>30</sup>. In cases of Child-Pugh C cirrhosis, their potential benefits remain unproven, prompting a judicious strategy due to adverse pharmacokinetics<sup>31</sup>. Moreover, aspirin, which has demonstrated potential in reducing the risk of HCC, may be continued in cirrhotic patients with other valid reasons for its use, without the need of discontinuation<sup>32</sup>. Rifaximin is indicated in secondary prophylaxis of hepatic encephalopathy and may reduce the risk of PH development in decompensated alcoholic cirrhosis, according to the preliminary data<sup>33</sup>.

## 2.6 Prevention of the First Decompensation

Liver decompensation is defined by the onset of clinically visible ascites, overt hepatic encephalopathy, or bleeding from esophageal or gastric varices. Bacterial infections, alcoholic hepatitis, acute viral hepatitis, liver damage caused by xenobiotics, or major surgical procedures can contribute to liver decompensation<sup>34,35</sup>.

Extrahepatic comorbidities in cirrhosis can negatively impact the disease outcome and require specific care. Currently, there is a lack of unequivocal evidence regarding the impact of sarcopenia on the natural course of compensated cirrhosis<sup>36</sup>. In patients with cACLD and CSPH or with gastroesophageal varices, NSBB should be administered for the prevention of the first liver decompensation, with carvedilol as the first-choice drug (up to 12.5 mg/day)<sup>37</sup>. In patients who cannot tolerate carvedilol, an attempt should be made with propranolol, provided that patients tolerate it (regular monitoring of blood pressure and pulse is required, with systolic blood pressure not falling below 90 mm Hg and pulse not dropping below 55/min)<sup>6</sup>. Patients with cACLD who are on NSBB therapy do not require screening upper endoscopy, as the presence or absence of EV does not affect the course of their treatment<sup>37,38</sup>. Patients with contraindications or intolerance to NSBB therapy and large esophageal or gastroesophageal varices (GOV1) should undergo endoscopic ligation<sup>39</sup>.

## 2.7 Cirrhosis Recompensation

Cirrhosis recompensation requires stable improvement in liver function tests (albumin, INR, bilirubin), removal/suppression/cure of the primary etiology of cirrhosis (viral elimination for hepatitis C, sustained viral suppression for hepatitis B, sustained alcohol abstinence for alcohol-induced cirrhosis) and resolution of ascites (off diuretics), portal encephalopathy (off lactulose/rifaximin), or absence of recurrent variceal bleeding (for at least 12 months)<sup>6</sup>. NSBBs should not be discontinued unless CSPH has disappeared<sup>6</sup>.

## 2.8 Further Decompensation of Cirrhosis

Compensated and decompensated cirrhosis represent the two major stages of cirrhosis. The initial stage, compensated cirrhosis, is often asymptomatic, with a median survival of  $\geq 12$  years<sup>40</sup>. Transition to the decompensated stage occurs at a rate of 5%-8% *per year*, causing rapid clinical deterioration after the first decompensating event<sup>40</sup>. CSPH is the key predictor of progression<sup>5,41</sup>. Further decompensation involves development of complications or a second

decompensating event (different from the first one), leading to advanced stages and rapid deterioration<sup>6,42</sup>. Liver transplantation should be considered once the first decompensation episode occurs.

### 2.9 Prevention of Further/New Decompensations in Patients with Ascites

The use of NSBBs in patients with ascites requires caution and should be avoided in hemodynamically unstable and/or patients with hepatorenal syndrome<sup>43</sup>. After achieving hemodynamic stability and resolving hepatorenal syndrome (HRS), reintroduction of NSBB may be considered. Propranolol is recommended at a dose of up to a maximum of 160 mg/day, with close monitoring of hemodynamic parameters and renal function<sup>44</sup>. In the absence of NSBB therapy, upper endoscopy is recommended to identify HRV, and in such cases, endoscopic ligation should be considered<sup>38</sup>. In patients with recurrent ascites, placement of a transjugular intrahepatic portosystemic shunt (TIPS) should be considered as it improves survival rates<sup>45</sup>. The first-line therapy for the prevention of recurrent variceal bleeding is a combination of NSBB and endoscopic variceal ligation (EVL)<sup>46</sup>. TIPS is the method of choice for patients who continue to bleed despite dual secondary prophylaxis<sup>45</sup>.

### 2.10 Infections in Decompensated Cirrhosis

Bacterial infections are a common cause of cirrhosis decompensation<sup>47</sup>. A minimal diagnostic approach in patients with acute decompensation of cirrhosis includes paracentesis with microbiological analysis of ascites, blood and urine cultures, chest x-ray, and skin examination. Bacterial infections should be promptly treated according to local epidemiological conditions, including the administration of broad-spectrum antibiotics in the cases of nosocomial infections when multidrug-resistant pathogens should be considered<sup>48</sup>.

### 2.11 Sarcopenia

Weakness, malnutrition, and sarcopenia significantly impact the survival of patients with decompensated cirrhosis<sup>49</sup>. Nutritional counseling,

daily energy intake of at least 35 kcal/kg body weight/day, protein intake of 1.2-1.5 g/kg body weight/day, and mandatory evening snack are recommended<sup>50,51</sup>. Regular physical activity should be maintained.

## 3 ENDOSCOPIC DIAGNOSIS AND TREATMENT OF ESOPHAGEAL VARICES

Esophageal varices (EV) represent pathologically dilated submucosal veins of the esophagus, connecting the portal and systemic circulation in patients with PH. The presence of EV indicates the presence of CSPH in patients with liver cirrhosis. According to the results of a recently published systematic review, the use of Baveno criteria has a negative predictive value of 99% (95% CI 99% to 100%), independently of the etiology of cirrhosis, reliably excluding HRV and thus eliminating the need of endoscopic examination<sup>6,52</sup>. Therefore, upper endoscopy is necessary in patients with cACLD who have LSM  $\geq 20$  kPa, or platelet count  $\leq 150 \times 10^9/L$  who are not on NSBB therapy, to exclude HRV<sup>6</sup>.

Esophageal varices may be categorized as small (varices are located just above the mucosal surface and collapse with air insufflation), medium (varices occupy less than 30% of the esophageal lumen and do not collapse with air insufflation), and large (varices occupy more than 30% of the lumen and touch each other)<sup>53</sup>. Endoscopic findings must include additional parameters such as the number of varices, location, and specifically the presence of stigmata indicating a high risk of variceal rupture (red patches, cherry spots, varix-on-varix)<sup>46</sup>. The Baveno consensus has adopted the simplest classification, dividing esophageal varices into small (<5 mm) and large (>5 mm) varices, and introducing the category of varices needing treatment (VNT), i.e., high-risk esophageal varices (HRV) (Figs. 2 and 3).

The latter includes large varices according to the Baveno classification (and medium-large according to earlier endoscopic classifications) and small varices with red signs or found in Child-Pugh C stage of cirrhosis, representing a clear indication for primary prophylaxis<sup>6,46</sup>.

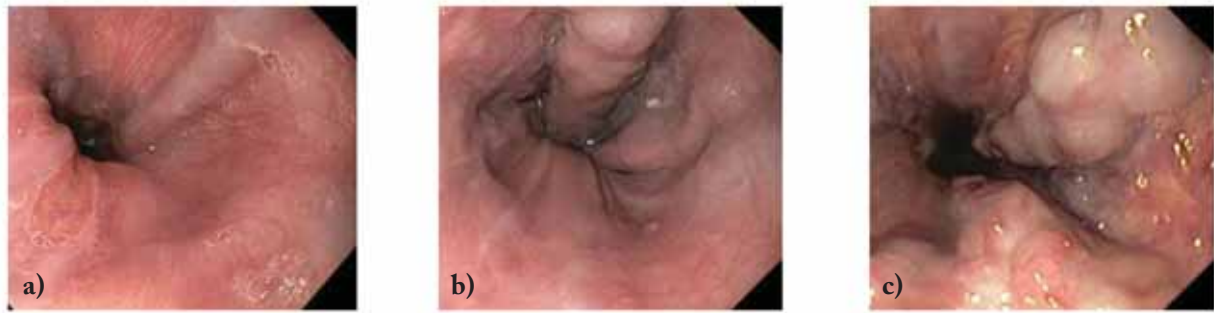


Fig. 2. Classification of esophageal varices according to size: a) small; b) medium; c) large.



Fig. 3. Red signs associated with the risk of variceal rupture: a) hemocystic lesions; b) red spots and wales; c) 'varix on varix'.

### 3.1 Primary Prophylaxis of Variceal Bleeding

In patients with cACLD and CSPH, the introduction of NSBB is necessary for the prevention of variceal bleeding<sup>37</sup>. The recommended dose of carvedilol is up to 12.5 mg/day, and for propranolol it is up to 320 mg/day in individuals without ascites or 160 mg/day in individuals with ascites<sup>6</sup>. Patients on NSBB should have regular blood pressure monitoring (with a systolic pressure not reducing below 90 mm Hg) and pulse monitoring (with a pulse not reducing below 55/min)<sup>6</sup>. In patients with HRV who cannot tolerate NSBB, endoscopic variceal ligation (EVL) should be performed<sup>46</sup>. EVL should be repeated at monthly intervals until variceal eradication is achieved. Afterward, upper endoscopy should be performed at intervals of 3-6 months during the first year of follow-up, and then depending on the patient's clinical condition<sup>46</sup>.

### 3.2 Acute Variceal Bleeding

Bleeding from EV represents the most serious complication in patients with uncontrolled PH, with

an estimated mortality of 20% within 6 weeks of bleeding onset<sup>54</sup>. In general, the treatment of patients with bleeding from varices is based on the same principles as when bleeding occurs from other sources in the gastrointestinal tract, with a few specifics. When replenishing volume, it is important to avoid aggressive fluid administration to prevent volume overload and a consequent increase in pressure in the portal system<sup>6</sup>. In hemodynamically stable patients without a history of cardiovascular disease and with hemoglobin values  $\leq 70$  g/L, a restrictive blood transfusion strategy is advisable, with a desirable post-transfusion hemoglobin value in the range of 70-90 g/L<sup>6,46</sup>. Antithrombotic therapy or proton pump inhibitors should be temporarily discontinued. Treatment with vasoactive drugs (terlipressin, somatostatin, octreotide) should be initiated as soon as possible<sup>6,46</sup>, as they reduce overall mortality, help control bleeding, reduce the recurrence of bleeding and the need of additional blood transfusion. Vasoactive drugs are administered for 2-5 days, after which NSBB is introduced. All patients with acute variceal bleeding should receive antibiotic prophylaxis, preferably with third-



generation cephalosporin (ceftriaxone 1 g/day) as they have an increased risk of bacterial infections, sepsis and death<sup>55</sup>. Upper endoscopy should be performed within 12 hours of a patient's presentation, or as soon as safely possible. In unstable patients, especially those with altered consciousness, endotracheal intubation is recommended before endoscopy to protect the airways from aspiration. The preferred method of hemostasis is endoscopic EVL, as it achieves better results than sclerotherapy<sup>56</sup>. In case of a failure of endoscopic hemostasis or in exceptional situations when endoscopic therapy is not available within 12 hours, balloon tamponade of esophageal varices (Sengstaken-Blakemore tube) or placement of esophageal metal stent can be used as a transient method of hemostasis<sup>46</sup>. The Sengstaken-Blakemore tube must be removed in 24 hours due to the risk of esophageal perforation, while the metal stent can remain for up to 7 days<sup>46</sup>. In the case of bleeding from gastric varices (gastroesophageal varix type 2, isolated gastric varices), the method of choice is intravariceal application of cyanoacrylate<sup>46</sup>. In case of failure of endoscopic hemostasis, the use of TIPS or balloon-occluded retrograde transvenous obliteration (BRTO) should be considered where available, especially in patients with contraindications for TIPS (e.g., with hepatic encephalopathy)<sup>6,57</sup>. In the case of bleeding from portosystemic gastropathy (PHG), hemostasis is achieved by using argon plasma coagulation, EBL, or radiofrequency ablation<sup>46</sup>. Finally, in patients with bleeding from esophageal varices, it is necessary to assess the risk of recurrent bleeding. Accordingly, in patients with Child-Pugh score B >7 and active bleeding on endoscopic examination, or Child-Pugh score C <14 regardless of bleeding status at the time of examination, or HVPG >20 mm Hg indicate a high risk of re-bleeding<sup>6</sup>. In these patients, preemptive TIPS should be considered, preferably within 72 hours of bleeding<sup>46</sup>. The presence of encephalopathy, acute-on-chronic liver failure (ACLF), or hyperbilirubinemia at the time of bleeding is not a contraindication for preemptive TIPS<sup>58</sup>. TIPS is also indicated in case of failure of initial endoscopic therapy or in case of recurrent bleeding that cannot be controlled endoscopically ('salvage TIPS'). In these patients, Child-Pugh score  $\geq 14$ , MELD >30, or lactate >12 mmol/L may indicate the futility of the procedure unless rapid liver transplantation is likely<sup>59</sup>. The outlined procedures are schematically presented in Figure 4.

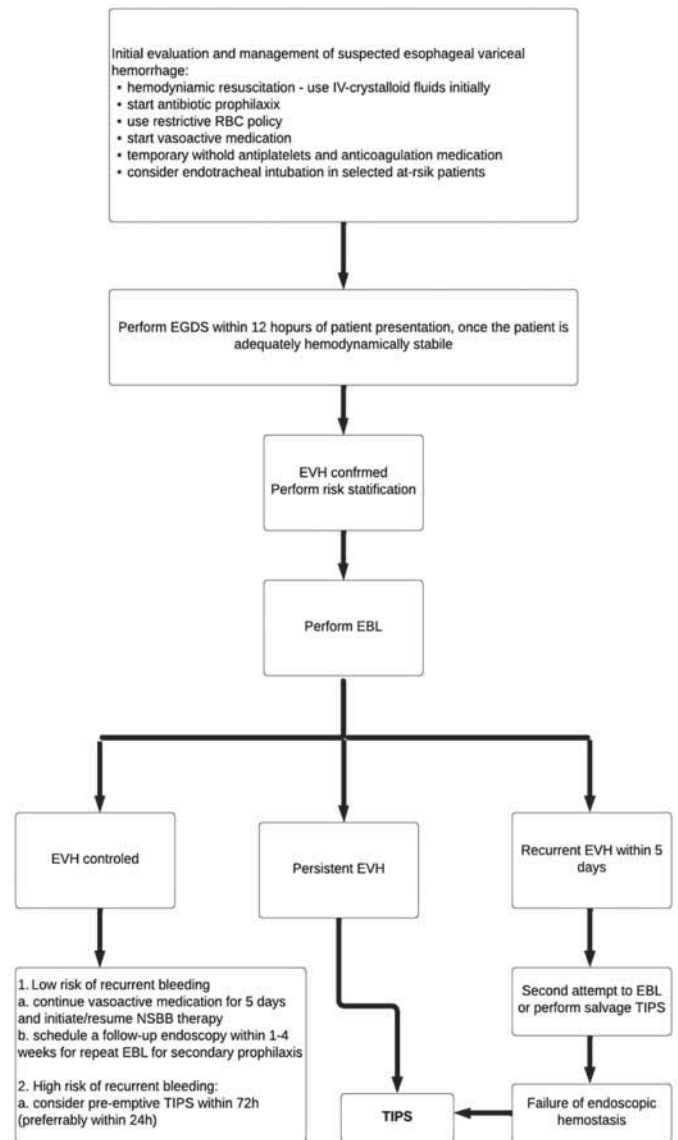


Fig. 4. The procedure in patients with acute bleeding from esophageal varices (modified according to reference 1).

iv = intravenous; EGDS = esophagogastroduodenoscopy; EBL = endoscopic band ligation; EVH = esophageal variceal hemorrhage; NSBB = non-selective beta-blockers; RBC = red blood cells; TIPS = transjugular intrahepatic portosystemic shunt

### 3.3 Prevention of Recurrent Bleeding from Esophageal Varices (Secondary Prophylaxis)

In patients with a history of bleeding from EV, secondary prophylaxis aimed at preventing recurrent bleeding should be performed. According to the recommendations of the European Society for

Gastrointestinal Endoscopy (ESGE), it is advisable to perform endoscopy and EVL at weekly or monthly intervals until variceal eradication is achieved<sup>46</sup>. In addition to endoscopic monitoring, conventional NSBB or carvedilol should be administered as well<sup>39</sup>.

Transjugular intrahepatic portosystemic shunt is the method of choice in patients who rebleed despite dual secondary prophylaxis<sup>58</sup>. In patients who cannot receive/tolerate EVL or NSBB, one of these therapeutic options should be applied, and in case of ascites TIPS should be considered<sup>45</sup>. In the case of bleeding from portohepatic gastropathy (PHG), argon plasma coagulation or hemostatic spray and NSBB should be applied<sup>46</sup>. In the event of recurrent bleeding and the need of transfusion despite endoscopic and NSBB therapy, TIPS placement should be considered<sup>60</sup>. In hemodynamic non-responders to NSBB, TIPS might be beneficial, but further data are needed<sup>61</sup>.

## 4 ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS

### 4.1 Ascites

Ascites represents the most common cause of decompensation in cirrhosis<sup>62</sup>. According to the amount of fluid in the abdominal cavity, ascites can be graded as 1) mild, 2) moderate, or 3) large<sup>48,63</sup>. The initial diagnostic workup for patients with newly developed ascites includes medical history, physical examination, abdominal ultrasound, laboratory assessment of liver and kidney function (albumin concentration, prothrombin time (PT/INR), bilirubin, blood urea nitrogen (BUN), creatinine), liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)), electrolyte concentration, complete blood count, inflammatory markers (C-reactive protein (CRP)), concentration and electrophoresis of serum proteins, and analysis of ascites. Diagnostic paracentesis should be performed in all patients with new onset of grade 2 and 3 ascites, as well as in all patients hospitalized due to worsening ascites or other complications of cirrhosis<sup>48,63,64</sup>. Ascites analysis should include neutrophil count, concentration of total proteins and albumin (with serum albumin concentration for calculation of serum-ascites albumin gradient (SAAG)), and ascites fluid culture<sup>48</sup>. SAAG  $\geq 1.1$  g/dL indicates portal hypertension as the most likely cause of ascites<sup>65</sup>. For grade 1 or mild ascites, there

are no data that treatment modifies natural history of the disease<sup>48</sup>. Moderate and severe (grade 2 and 3) ascites require treatment, which is based on sodium restriction and administration of diuretics. Moderate sodium restriction is recommended with the intake of about 80–120 mmol of sodium, corresponding to around 4.6–6.9 g of salt *per day*<sup>48,66,67</sup>. Since secondary hyperaldosteronism represents the key pathogenetic mechanism responsible for renal sodium retention, anti-mineralocorticoid drugs are the mainstay of ascites treatment, i.e., spironolactone (which is used in Croatia) or canrenone and K-canrenoate (which are currently unavailable in Croatia)<sup>68,69</sup>. Spironolactone is initiated at a dose of 100 mg daily, which can be increased by 100 mg every 72 hours if there is an inadequate response, up to a maximum dose of 400 mg<sup>48,63,64</sup>. Amiloride is recommended instead of aldosterone antagonists in case of side effects, most commonly gynecomastia, but is currently unavailable in Croatia. We recommend substitution of spironolactone by eplerenone as the only available alternative in Croatia, although literature data on its efficacy are scarce<sup>48,70</sup>. In case of ineffectiveness of aldosterone antagonists (weight loss  $< 2$  kg in one week or occurrence of hyperkalemia), furosemide should be added at a dose of 40 mg/day with a gradual increase to a maximum of 160 mg/day<sup>48</sup>. Patients with long-term or recurrent ascites (occurring in three or more episodes within 12 months) should be treated with a combination of spironolactone and furosemide<sup>71,72</sup>. In patients with a poor response to furosemide, torsemide can be used<sup>73</sup>. The maximum recommended weight loss is 0.5 kg/day in patients without edema and 1 kg/day in patients with edema<sup>74</sup>. After ascites resolution, the diuretic dose should be tapered to the lowest effective dose<sup>48</sup>. Serial biochemical monitoring of serum creatinine, potassium, and sodium is recommended, more frequently during the first month of diuretic therapy<sup>48</sup>. Measurement of urinary sodium excretion is recommended only in patients who do not respond to diuretic therapy with sodium intake restriction<sup>48,72</sup>. It is recommended to control gastrointestinal bleeding and correct abnormalities such as renal impairment, hepatic encephalopathy, hyponatremia, or potassium concentration alterations (hyperkalemia or hypokalemia) before initiating diuretic therapy<sup>48</sup>. Furosemide should be discontinued in case of severe hypokalemia ( $K < 3$  mmol/L), and spironolactone in case of severe hyperkalemia ( $K > 6$

mmol/L)<sup>48</sup>. Diuretics should be discontinued in case of severe hyponatremia ( $\text{Na} < 120\text{--}125$  mmol/L), acute kidney injury, worsening of hepatic encephalopathy, or muscle cramps<sup>48</sup>. Diuretic therapy should also be stopped in patients with refractory ascites if urinary sodium excretion with diuretics does not exceed 30 mmol/day<sup>48,63</sup>. In patients with large (grade 3) ascites, large volume (>5 L) paracentesis (LVP) represents the treatment of choice<sup>48</sup>. All the amount of ascites should be removed in a single session. LVP should be followed by plasma volume expansion using human albumin at a dose of 8 g *per* liter of removed ascites<sup>48,75</sup>. The removal of volumes less than 5 L is associated with a lower risk of post-paracentesis circulatory dysfunction, but albumin administration is also recommended in these cases. In patients with large (grade 3) ascites treated with LVPs, diuretic therapy should be continued to prevent re-accumulation of ascites<sup>76</sup>. In patients with refractory ascites, repeated LVPs with albumin infusion (8 g/L of removed ascites) represent the therapy of choice<sup>48</sup>. Refractory ascites is one that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy, which includes the maximum recommended doses of spironolactone (400 mg) and furosemide (160 mg) for at least one week, with a salt restricted diet (<90 mmol of sodium/day)<sup>63,64</sup>. In patients with refractory ascites treated by repeated LVPs with albumin infusion, diuretic therapy should be discontinued, unless urinary sodium excretion with diuretics exceeds 30 mmol/day<sup>63</sup>. Data on the use of non-selective beta-blockers (NSBB) in patients with refractory ascites are contradictory and they should be administered with caution, while high doses (e.g., propranolol >80 mg/day) should be avoided<sup>48</sup>. In patients with impaired blood clotting (international normalized ratio INR >1.5 and platelet count <50x10<sup>9</sup>/L), bleeding at the puncture site is very rare, which is why routine use of fresh frozen plasma or pooled platelets is not recommended<sup>48,77</sup>. The most common contraindications for paracentesis are patient non-compliance, skin infection at the intended puncture site, pregnancy, significant bowel distension, and severe coagulopathy (disseminated intravascular coagulation)<sup>48</sup>. In patients with recurrent and refractory ascites, the use of TIPS should be considered. TIPS better controls ascites in patients with refractory and recurrent ascites compared to LVPs, but it is also associated with a higher incidence of hepatic encephalopathy<sup>48</sup>.

## 4.2 Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) represents a bacterial infection of ascites in the absence of an intra-abdominal source of infection amenable to surgical treatment. The diagnosis of SBP is based on diagnostic paracentesis and is established on the finding of >250 neutrophils/mm<sup>3</sup> of ascites<sup>78</sup>. Diagnostic paracentesis should be performed in all patients with cirrhosis and ascites immediately following hospital admission to exclude SBP. Diagnostic paracentesis is also necessary for patients with signs of gastrointestinal bleeding, shock, gastrointestinal symptoms, fever, or other signs of systemic inflammation, as well as for patients with worsening liver or kidney function or encephalopathy. In all patients with suspected SBP, ascites and blood cultures should be performed before starting antibiotic therapy to allow for subsequent correction of antibiotic regimen if required. Patients with negative cultures and an elevated neutrophil count  $\geq 250$  cells/mm<sup>3</sup> have microbiologically negative SBP, and their treatment does not differ from patients with positive ascites cultures. Patients with bacterascites (positive bacterial cultures with a normal neutrophil count, i.e., <250 cells/mm<sup>3</sup>) and signs of systemic inflammation or infection should be treated with antibiotics<sup>48</sup>. Patients with bacterascites without signs of systemic inflammation or infection should undergo repeated paracentesis. In case of a repeatedly positive ascites culture, such patients should also be treated with antibiotics. In patients with a very high neutrophil count and/or protein concentration in ascites, or multiple bacteria in ascites culture, or a poor response to therapy, secondary bacterial peritonitis should be suspected.

Empirical intravenous antibiotic therapy should be initiated immediately upon diagnosis of SBP. For patients with community-acquired SBP, third-generation cephalosporins are the treatment of choice<sup>48</sup>. For patients with healthcare-associated or nosocomial infections and a higher risk of antibiotic resistance, the use of piperacillin-tazobactam is recommended in areas with a low prevalence of multidrug-resistant bacteria, while carbapenems are the drugs of choice in areas with a high prevalence of enterobacteria producing beta-lactamases<sup>48</sup>. In areas with a high prevalence of gram-positive multidrug-resistant bacteria, the recommended treatment for SBP is a combination of carbapenems with a glycopeptide or daptomycin or linezolid.

The efficacy of antibiotic therapy in the treatment of SBP should be checked by repeated paracentesis 48 hours after the start of antibiotic therapy. Lack of response to the first-line antibiotic therapy is indicated by: (a) an inadequate decrease in neutrophil count (by <25% from initial values), or (b) an increase in neutrophil count, or (c) worsening clinical symptoms and signs of infection. The recommended duration of antibiotic therapy for SBP is at least 5-7 days. In the treatment of SBP with antibiotics, the use of albumin at a dose of 1.5 mg/kg of body weight at the time of diagnosis and 1 g/kg on the third day of treatment is recommended<sup>48</sup>. Proton pump inhibitors may increase the risk of developing SBP, so their use should be avoided with the exception of patients with a clear indication for their use.

After the first episode of SBP, patients should be considered for liver transplantation. Prophylaxis for SBP is recommended in patients at high risk of developing SBP, such as those with a history of SBP, gastrointestinal bleeding, and patients with a low protein concentration in ascites<sup>48</sup>. Primary prophylaxis for SBP is indicated in patients with advanced cirrhosis (Child-Pugh score  $\geq 9$  and bilirubin 50 micromol/L) and a protein concentration in ascites of less than 15 g/L, with impaired kidney function (serum creatinine  $\geq 115$  micromol/L, urea  $\geq 8.9$  mmol/L, or hyponatremia  $\leq 130$  mEq/L)<sup>79-82</sup>. Primary prophylaxis is performed using norfloxacin at a dose of 400 mg/day until long-term improvement or disappearance of ascites. Secondary prophylaxis for SBP is recommended for patients who have survived an episode of SBP using norfloxacin at a dose of 400 mg/day<sup>79,83,84</sup>.

## 5 HEPATORENAL SYNDROME

### 5.1 Definition and Classification

Hepatorenal syndrome (HRS) is one of the phenotypes of renal dysfunction that occurs in patients with liver disease, especially those with cirrhosis and ascites. In patients with decompensated cirrhosis, HRS is often precipitated by liver-related factors (alcohol, drugs, inflammation) or non-liver-related factors (bacterial infections or bacterial translocations). Diagnostic criteria for HRS include the following components<sup>85</sup>:

- presence of cirrhosis; acute liver failure; acute-on-chronic liver failure (ACLF);
- increase in serum creatinine  $\geq 26.5$   $\mu\text{mol/L}$  (0.3 mg/dL) within 48 hours or  $\geq 50\%$  increase in initial serum creatinine within 7 days or urine volume  $\leq 0.5$  mL/kg over 6 hours;
- lack of partial or complete response to diuretic withdrawal and volume expansion with albumin after 2 days (recommended dose of albumin is 1 g/kg body weight *per* day, up to a maximum of 100 g/day);
- absence of shock;
- current/recent absence of nephrotoxic drugs; and
- absence of parenchymal kidney disease (proteinuria  $> 500$  mg/day, microhematuria ( $> 50$  red blood cells), urinary biomarkers of injury (if available), and/or abnormal ultrasound findings of the kidneys\* (\*this criterion is not possible in pre-existing kidney disease).

The classification of HRS includes phenotypes of renal dysfunction related to acute kidney injury (Fig. 5). However, it can also relate to renal dysfunction within the context of subacute chronic kidney disease, as indicated in Table 2<sup>85</sup>.

Table 2. Classification of hepatorenal syndrome

HRS type		Criteria
HRS-AKI		a) serum creatinine increase $\geq 26.5$ $\mu\text{mol/L}$ in the last 48 h/OR b) urine output $< 0.5$ mL/kg/h over 6 hours/OR c) $\geq 50\%$ serum creatinine increase in the last 3 months
HRS-NAKI	HRS-AKD	a) eGFR $< 60$ mL/min/1.73 m <sup>2</sup> for $< 3$ months, with no other cause of kidney disease b) $< 50\%$ increase in serum creatinine within 3 months
	HRS-CKD	a) eGFR $< 60$ mL/min/1.73 m <sup>2</sup> for $> 3$ months, with no other cause of kidney disease

HRS = hepatorenal syndrome; AKD = acute kidney disease; AKI = acute kidney injury; CKD = chronic kidney disease; NAKI = non-acute kidney injury



Acute kidney disease in cirrhosis represents the spectrum of different AKI phenotypes, including the HRS-AKI, but also acute tubular necrosis AKI (ATN-AKI), prerenal, and post-renal AKI, and they should be precisely assessed, as the treatment and prognosis are not the same. In addition to this, the increasing prevalence of NAFLD cirrhosis that is accompanied by metabolic comorbidities and their complications might lead to more cases of AKI superimposed on CKD caused by diabetic nephropathy, and this should be appreciated when considering treatment options.

## 5.2 Pathogenesis of Hepatorenal Syndrome

The pathogenesis of HRS involves hemodynamic changes in the context of decompensated liver disease and structural components of renal damage. In addition to renal hypoperfusion resulting from microcirculation dysfunction due to splanchnic arterial vasodilation and inadequate cardiac output, the pathophysiology of HRS is complemented by components of systemic inflammation, oxidative stress, and tubular damage caused by bile acids (Fig. 6)<sup>87-92</sup>. Bacterial translocation is the primary mechanism through

which circulatory dysfunction develops in HRS under conditions of portal hypertension, as well as infectious complications such as spontaneous bacterial peritonitis<sup>91</sup>. Translocation stimulates a signalling pathway in which pathogen-associated molecular pattern molecules (PAMPs) lead to the activation of monocytes and the release of proinflammatory cytokines such as TNF $\alpha$ , IL-6, and IL-1 $\beta$ <sup>90</sup>. As a result, the synergistic effect of the signalling pathway involving PAMPs and damage-associated molecular pattern molecules (DAMPs) released by the liver promotes changes in the epithelial cells of the proximal tubules of the kidney, leading to enhanced absorption of sodium and chloride in renal tubules. This, in turn, activates the renin-angiotensin system and reduces the glomerular filtration rate<sup>91,93</sup>. Under these conditions, pronounced cholestasis further worsens renal function by intensifying inflammation and/or microcirculatory dysfunction<sup>92</sup>. Alternatively, the direct effect of bile acids damages tubules. In conclusion, the mechanism of renal injury in the context of HRS-AKI is a result of renal hypoperfusion, the influence of inflammation and microvascular dysfunction, and the direct damage to renal tubules (Fig. 6).

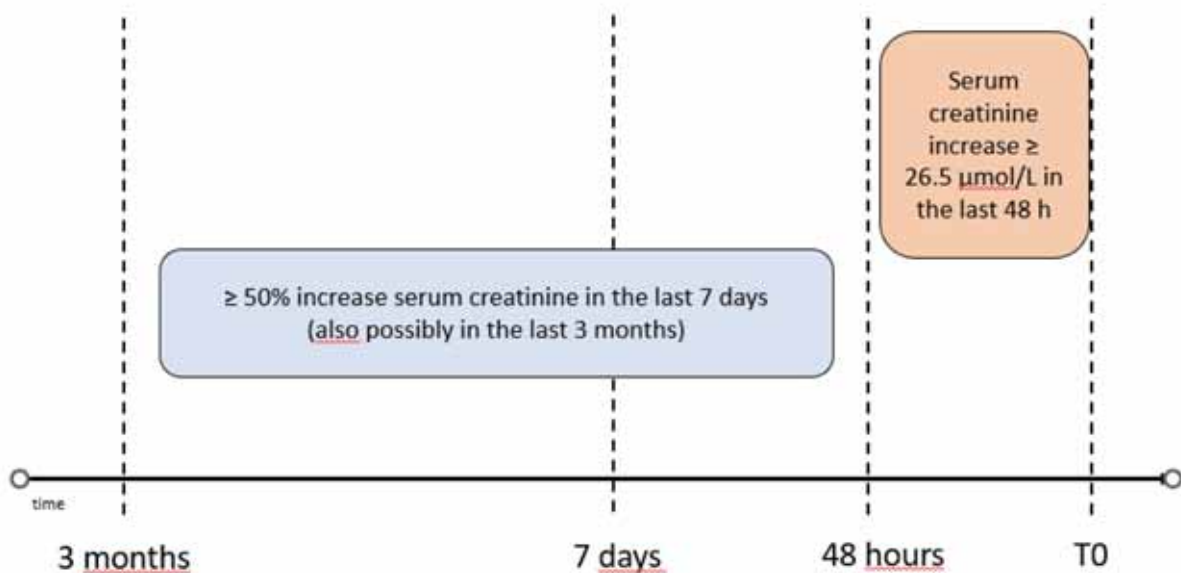


Fig. 5. Acute kidney injury criteria based on absolute and percentage increase of creatinine in relation to the time of injury presentation ( $T_0$ ) (adapted from: Angeli *et al.* *J Hepatol.* 2015 Apr;62(4):968-74)<sup>86</sup>.

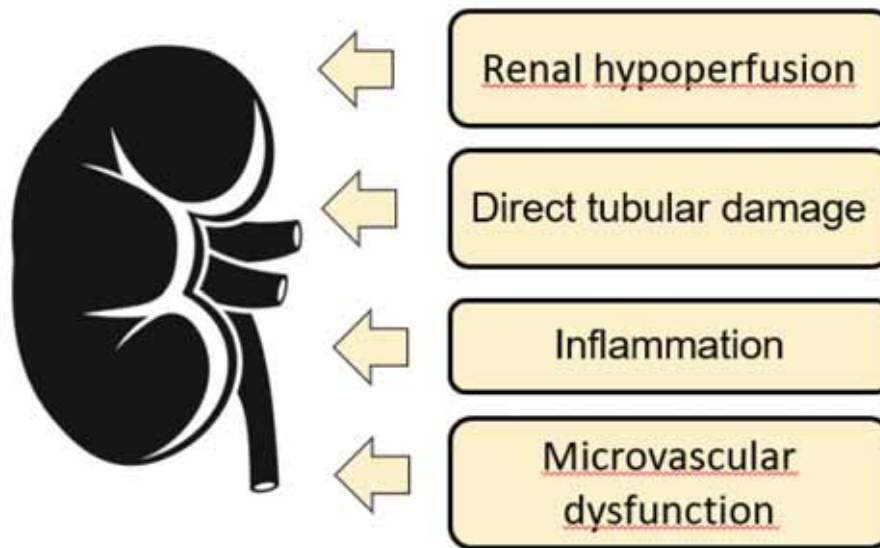


Fig. 6. Mechanisms of renal injury in patients with hepatorenal syndrome-acute kidney injury (adapted from: Angeli *et al.* *J Hepatol.* 2019 Oct;71(4):811-22)<sup>85</sup>.

### 5.3 Treatment of Hepatorenal Syndrome

#### 5.3.1 Vasoconstrictor drugs

The foundation of HRS therapy, along with albumin replacement, involves vasoconstrictor drugs that induce splanchnic vasoconstriction, thereby improving renal perfusion (Fig. 7)<sup>94</sup>.

Terlipressin, a vasopressin analog, is commonly used in the treatment of HRS-AKI<sup>95</sup>. It is recommended to administer it in combination with albumin<sup>48</sup>. The dose of albumin in HRS therapy is not clearly defined, and intravenous albumin is commonly given at a dose of 20-40 g/day. Albumin and terlipressin therapy increases the circulating volume of the body, which has a favorable effect on the reduced cardiac output seen in HRS, and extends the short-term survival of patients with HRS<sup>96-98</sup>. Terlipressin can be administered in the form of intravenous boluses at an initial dose of 0.5-1 mg every 4-6 hours, with the possibility of gradual dose escalation after 48 hours, up to a maximum of 2 mg every 4-6 hours in the case of a decrease in baseline serum creatinine <25%<sup>99</sup>. Additionally, terlipressin can be administered as a continuous infusion at a dose of 2 mg/day, with almost similar therapeutic response and a lower rate of side effects compared to intravenous boluses<sup>99-101</sup>. The most common side effects of terlipressin treatment are diarrhea, abdominal pain, heart failure, and cardiovascular ischemic complications

occurring in 45%-46% of patients treated with intravenous boluses<sup>101</sup>. Cardiovascular complications are the most common reason for discontinuing therapy (20%), making it necessary to perform an ECG in all patients before starting treatment. The decision to treat in the intensive care unit is made individually for each patient. Up to 20% of patients who respond to therapy will experience HRS again, but repeat therapy is often successful<sup>102</sup>.

Other options include intravenous administration of norepinephrine and the use of midodrine (midodrine is currently unavailable in Croatia) with subcutaneous or intravenous administration of octreotide, both again in combination with albumin. The most important factors for a poor response to vasoconstrictors are baseline serum creatinine levels, the degree of inflammation, and the severity of cholestasis<sup>103,104</sup>. The higher the baseline serum creatinine values, the poorer is the response to terlipressin and albumin therapy, likely reflecting existing damage to renal parenchyma<sup>105</sup>. Treatment is continued until a complete response to therapy is achieved (serum creatinine below 133  $\mu\text{mol/L}$  (1.5 mg/dL)) or for a maximum of 14 days in the case of a partial response to therapy (serum creatinine drop of  $\geq 50\%$  with the final value still greater than 133  $\mu\text{mol/L}$  (1.5 mg/dL)) and in the case of a complete lack of response to therapy<sup>48</sup>.

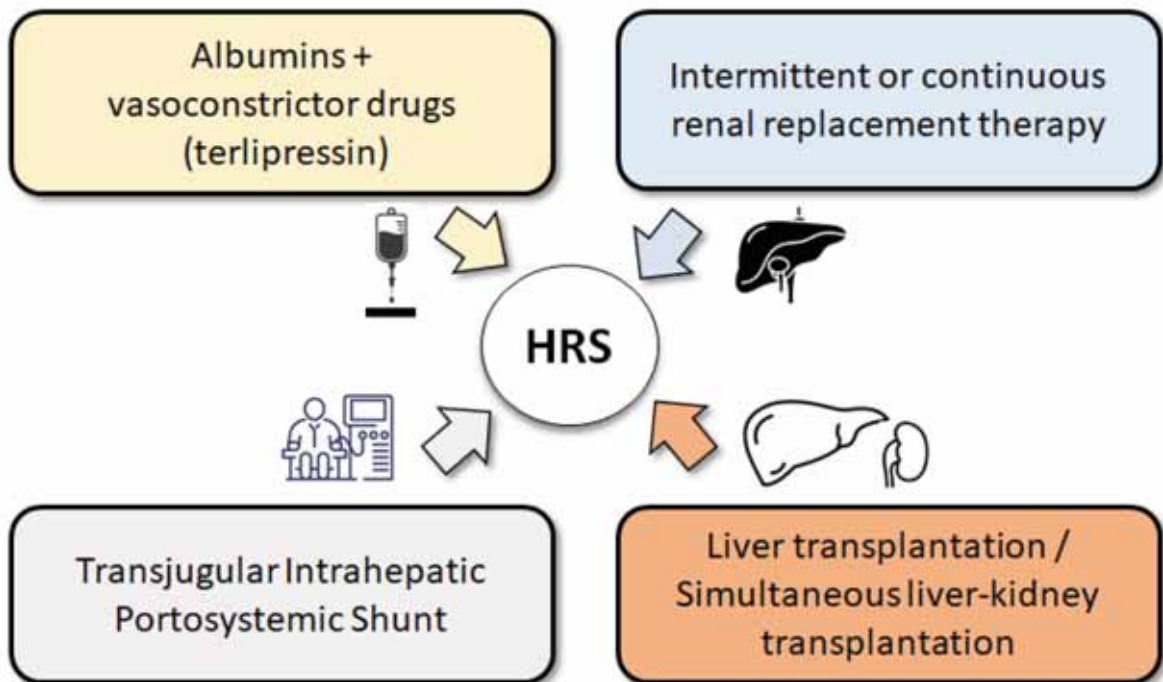


Fig. 7. Therapeutic options in the treatment of hepatorenal syndrome.

### 5.3.2 Transjugular intrahepatic portosystemic shunt (TIPS)

The placement of a transjugular intrahepatic portosystemic shunt (TIPS), in addition to reducing portal vein pressure, also increases effective arterial flow, leading to improved renal function. According to the meta-analysis that included 9 studies with 128 patients with HRS as classified according to the old nomenclature, TIPS resulted in short-term and 1-year survival of 72% and 47% patients with HRS1 and 86% and 64% with HRS2. Renal function improved in 93% of patients with HRS1, and 83% of those with any type of HRS, but hepatic encephalopathy developed in 49% of patients<sup>105</sup>. This limited evidence suggests a potential survival benefit of TIPS, which might represent a potential therapeutic option in the treatment of HRS, especially in patients with ascites, who are unresponsive to medical treatment, unsuitable for liver transplantation, or for prophylaxis of a HRS relapse. However, for some patients, the placement of TIPS is limited by the severity of liver failure, with an increased risk of worsening portal encephalopathy and exacerbating cardiomyopathy<sup>107,108</sup>. At this point,

more data are needed to make more evidence-based statement regarding the indications for TIPS in the context of HRS.

### 5.3.3 Renal replacement therapy

In patients with HRS, renal replacement therapy (RRT) is a therapeutic option for those who do not respond to vasoconstrictor and albumin therapy, as well as for all patients with end-stage renal disease. Initiating RRT should be based on clinical indications such as worsening renal function, electrolyte disturbances such as severe acidosis, hyponatremia, or hyperkalemia not corrected by conservative measures, intolerance to diuretics, or increased volume overload. Continuous renal replacement therapy (CRRT) is the preferred modality over intermittent dialysis in hemodynamically unstable patients<sup>109</sup>.

### 5.3.4 Liver transplantation and simultaneous liver-kidney transplantation

The best therapeutic option for a patient with HRS is liver transplantation (LT) since it offers a clear survival benefit<sup>110</sup>. In cases where it is unlikely that

renal function will recover after liver transplantation, simultaneous liver-kidney transplantation (SLKT) should be considered. SLKT is indicated in patients with liver cirrhosis and chronic kidney disease in the following clinical situations: (a) estimated glomerular filtration rate (GFR)  $\leq 40$  mL/min, (b) proteinuria  $\geq 2$  g/day, (c) kidney biopsy findings with  $>30\%$  global glomerulosclerosis or  $>30\%$  interstitial fibrosis, and (d) inherited metabolic disease. Additionally, SLKT is an option for treating patients with liver cirrhosis and irreversible acute kidney injury (AKI), including HRS-AKI refractory to medical therapy in the following situations: (a) AKI on renal replacement therapy lasting for more than 4 weeks, and (b) estimated GFR  $\leq 35$  mL/min or measured GFR  $\leq 25$  mL/min for  $\geq 4$  weeks<sup>111</sup>. In patients with HRS-AKI on the liver transplantation waiting list, a response to medical therapy due to a decrease in serum creatinine and consequently the Model for End-Stage Liver Disease (MELD) score may delay transplantation.

#### 5.4 Prevention of Hepatorenal Syndrome

The prevention of HRS is generally based on preventing liver decompensation and, pharmacologically, on albumin therapy (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) in patients who develop spontaneous bacterial peritonitis. Additionally, preventing spontaneous bacterial peritonitis with norfloxacin therapy (400 mg/day) is recommended<sup>79,112</sup>.

## 6 HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a common and one of the most severe complications of liver diseases. It comprises a spectrum of neuro-psychiatric conditions found in patients with acute and chronic liver failure and portosystemic shunts. The incidence and prevalence of HE correlate with the severity of liver disease. It appears over the course of life in 50%-70% of patients with liver cirrhosis, with a high risk of recurrence<sup>113,114</sup>. If the underlying liver disease is not successfully treated, HE is associated with a one-year survival rate of 42%-54% in patients<sup>115</sup>. Significantly more than other complications of liver disease, HE burdens healthcare resources and requires hospital care<sup>116</sup>.

### 6.1 Pathogenesis

The mechanisms causing brain dysfunction in liver failure are not fully understood. They may reflect any condition, e.g., reversible metabolic encephalopathy, impairment of neurotransmitter systems, alterations in brain metabolism, changes in blood-brain barrier permeability, brain atrophy, brain edema, weakening of cerebral perfusion, or any combination of these conditions. Ammonia is considered the most responsible neurotoxin for the development of HE, with its levels elevated in nearly 80% of HE patients<sup>117</sup>. Other toxins, such as mercaptans or short-chain fatty acids, may enhance the toxicity of ammonia. Additionally, the role of inhibitory neurotransmission *via* gamma-aminobutyric acid (GABA) receptors has been established. Sepsis, neuroinflammatory response, and changes in gut microbiota also appear to be additional factors in the development of altered brain function in advanced liver disease.

### 6.2 Classification

According to the visibility of clinical manifestations, HE is divided into covert (CHE) and overt (OHE). The prevalence of CHE in patients with liver cirrhosis is 20%-80% and it is not easily recognizable during clinical examination<sup>118</sup>. Tools for its detection include the use of psychometric and neurophysiological tests, attention tests, working memory tests, psychomotor speed, and visual-spatial abilities, as well as electrophysiological and other functional measurements of brain activity<sup>119</sup>. Over a 5-year follow-up, 86% of patients with CHE develop OHE<sup>120</sup>. It is recommended to test all patients with liver cirrhosis without OHE at least every 6 months using two tests simultaneously, especially in patients with subtle neurocognitive changes noticed by the patient or their surroundings (e.g., sleep disturbances, decreased attention and short-term memory, changes in work capacity, or a tendency to injury)<sup>121,122</sup>. Since none of the available tests is highly specific for CHE, it is necessary to exclude the presence of other overlapping factors (e.g., other neuropsychiatric disorders, consumption of psychoactive drugs or alcohol)<sup>123</sup>.

The clear clinical visibility and characteristics of various neuropsychiatric disorders define the presence and severity of OHE symptoms. OHE occurs in 30%-45% of patients with liver cirrhosis and 10%-



Table 3. West Haven classification of hepatic encephalopathy

		Changes in the state of consciousness	Psychological and intellectual difficulties	Neuromuscular symptoms
Covert hepatic encephalopathy (CHE)	Minimal (MHE)	No	Changes measurable only by neurophysiological and neuropsychological tests, slight slowdown in visual perception, working ability and driving	
	1	Mild mental slowdown	Some cognitive/behavioral decay with respect to his/her standard on clinical examination or to the caregivers Personality changes, euphoria, irritability, anxiety, depression, impaired attention, altered sleep rhythm	Impairment of fine motor skills, mild tremor, coordination disorder
Overt hepatic encephalopathy (OHE)	2	Increased fatigue, moderate confusion, apathy and lethargy	Changes in mood and behavior, apathy and lethargy, cognitive dysfunction, mild disorientation in space and time	Flapping tremor, asterixis, ataxia, uncoordinated movements, speech difficulties
	3	Somnolence, stupor	Confusion, significant disorientation in time and space, amnesia, incoherent speech, bizarre behavior	Rigor, nystagmus, clonus, positive Babinski sign, hypo- or hyper-reflexia
	4	Coma		

50% of patients with TIPS<sup>113</sup>. The most commonly used classification of the severity of neuropsychiatric disorders is the West-Haven (WH) classification (Table 3), and in patients with WH stages 3 and 4, the Glasgow Coma Scale (GCS) is additionally used<sup>122</sup>.

The course of HE can be episodic, recurrent (HE episodes occur within a six-month interval), or persistent (permanently present behavioral changes intertwined with episodes of overt HE). The precipitating factor for the onset of an HE episode can be identified in almost 70%-80% of patients. Most commonly, it involves infections, electrolyte and metabolic imbalance, bleeding in the digestive tract,

hypovolemia, constipation, worsening renal function, hypoxia, hypoglycemia, diuretic overdose, sedative use, alcohol consumption, and less frequently hepatocellular carcinoma or thrombosis of the liver venous system<sup>122</sup>.

### 6.3 Diagnostic Approach

The examination includes routine clinical, laboratory, and imaging tests to define the stage of liver disease and its complications, the presence of neuropsychiatric disorders in OHE, the application of psychometric and neurophysiological tests to determine CHE, and determination of ammonia levels. Due to its low specificity, an elevated level of ammonia should

not be used as a screening tool for HE in asymptomatic patients or those with neuropsychiatric changes in the absence of liver disease or portosystemic shunting. The diagnosis of HE is also based on excluding the presence of other conditions that can affect the patient neuropsychiatric status (e.g., medication use, trauma, recent alcohol consumption, effects of metabolic imbalance, hypoglycemia, psychiatric changes). Such non-hepatic causes are present in >20% of patients with liver cirrhosis. They should be especially suspected in patients with liver cirrhosis and normal ammonia levels and those who do not respond to at least minor clinical improvement with therapy aimed at lowering ammonia levels<sup>119</sup>. For further investigation of non-hepatic causes, it is necessary to perform a CT or MRI of the brain and targeted laboratory tests.

#### 6.4 Treatment Algorithm

Treatment is indicated for all patients with OHE and for patients in whom changes associated with CHE have been proven<sup>122,124</sup>. Primary prevention is only indicated in patients with cirrhosis and clearly defined risk factors for an episode of HE (variceal bleeding, TIPS)<sup>115,125</sup>. Due to the high risk of recurrent OHE episodes (47% annually), routine secondary prevention of HE episodes is performed. The application of secondary prevention is carried out either lifelong or until liver transplantation.

Measures need to be taken to control the progression of the underlying liver disease and treat its complications, exclude and treat any other (non-hepatic) factors affecting neuropsychiatric status changes, treat the precipitating factor of HE, provide nutritional support, and administer medications to reduce ammonia levels (Fig. 8). Patients with higher grades of HE (WH grades 3 and 4 or GCS <8), who are at risk of aspiration, require intensified monitoring. In almost 90% of patients, OHE symptoms can be resolved by correcting the precipitating factor<sup>122</sup>. Patients with HE can be extremely agitated, and until the targeted HE therapy takes effect, they may pose a risk to themselves and others. They are highly sensitive to excessive sedation, especially benzodiazepines due to the increased concentration of benzodiazepine receptor ligands in the brain. The application of reasonable levels of mobility restriction in such cases may be a safer treatment option than pharmacological measures. If sedation is needed, haloperidol appears to be a safer option than benzodiazepines<sup>126</sup>.

##### 6.4.1 Nutritional support

Approximately 75% of patients with HE have moderate to severe protein-calorie malnutrition with loss of muscle mass and energy reserves<sup>127</sup>. Therefore, most patients with HE will meet the criteria for nutritional support with 4-6 meals *per* day at intervals no longer than 3-6 hours and one late-night meal rich in complex carbohydrates. The recommended daily calorie intake is 35-40 kcal/kg of ideal body weight (IBW) with a high proportion of carbohydrates (40%-60%), slightly less lipids (25%-30%), and protein intake should be 1.2-1.5 g/kg IBW/day<sup>50</sup>. Low-protein diets (0.8 g/kg IBW/day) should be avoided, except for exceptional cases and for a maximum of a few days in patients with stage 4 HE or in the presence of intractable gastrointestinal bleeding. In the case of protein intolerance, it is possible to restrict protein intake while simultaneously supplementing with oral branched-chain amino acids (BCAA). If confirmed deficiencies of vitamins and micronutrients exist, they should be replenished, particularly in the case of thiamine deficiency in Wernicke's encephalopathy and hypokalemia (due to its impact on ammonia metabolism).

##### 6.4.2 Non-absorbable disaccharides (lactulose, lactitol)

In the first line of treatment for episodic OHE and CHE, therapy begins with non-absorbable disaccharides – lactulose which is used in Croatia, or lactitol where available. These are also the most commonly used drugs for secondary prevention of OHE and primary prevention of HE in patients with variceal bleeding<sup>122,128</sup>.

The optimal dose of the drug is 15-40 mL 2-4 times a day, with dose titration to achieve 3-4 softer stools *per* day. If the patient cannot tolerate oral intake, enemas can be administered.

In OHE, lactulose is effective in 70%-80% of patients<sup>128</sup>. The risk of a poorer response to lactulose therapy is associated with a higher Model of End-Stage Liver Disease (MELD) score, leukocytosis, hyponatremia, arterial hypotension, and hepatocellular carcinoma<sup>129</sup>. Overdosing can lead to dehydration, electrolyte imbalance, and worsening of HE symptoms<sup>130</sup>. The primary challenge of long-term lactulose use is patient non-compliance, which often (in 37% of patients) results in the need of early re-hospitalizations due to HE recurrence<sup>130</sup>.

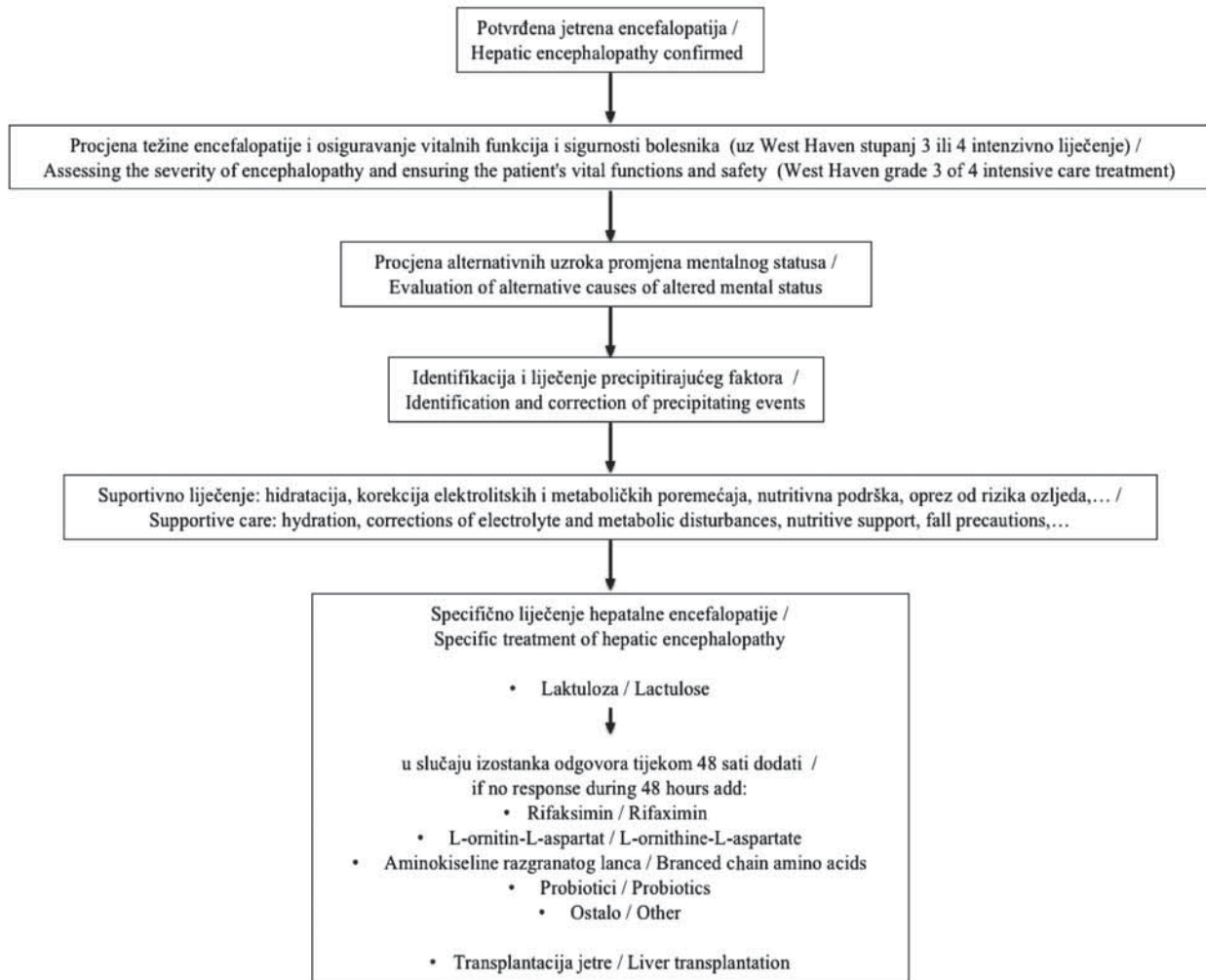


Fig. 8. Algorithm for the management of hepatic encephalopathy.

### 6.4.3 Rifaximin

Rifaximin in combination with lactulose is indicated for secondary prophylaxis of recurrent OHE. Additionally, treatment with rifaximin is suggested for patients who do not show improvement in HE status within 48 hours (in addition to lactulose), or those who cannot tolerate lactulose or lactitol. In patients with liver cirrhosis and previous episodes of OHE, rifaximin may also be considered for HE prophylaxis before the elective placement of TIPS<sup>122,123</sup>. Combined therapy is associated with the recovery of HE symptoms, prevention of recurrent HE episodes, and a shorter duration of hospitalization<sup>124,125,131</sup>.

The recommended dose of rifaximin is 2x550 mg or 3x400 mg daily. Compared to lactulose, the use of

rifaximin is associated with better tolerability, but at a higher treatment cost. It should be noted that the use of rifaximin monotherapy is less researched, considered less effective, and the safety of its use has been examined in therapy lasting for up to 24 months<sup>132</sup>.

### 6.4.4 L-ornithine-L-aspartate (LOLA)

In the second line, for patients with insufficient effectiveness or intolerance to standard therapy or secondary prophylaxis of HE with non-absorbable disaccharides, the use of L-ornithine-L-aspartate (LOLA) is recommended. Depending on the indication (presence of side effects or ineffectiveness), combined therapy (with lactulose) or monotherapy with LOLA can be considered.

The effectiveness of LOLA in reducing blood ammonia levels and recovering HE symptoms has been demonstrated in many controlled studies and meta-analyses for both formulations (parenteral (IV) and oral (PO))<sup>133-135</sup>. Controlled studies comparing the use of LOLA with lactulose or rifaximin have shown comparable or favorable effects of LOLA<sup>136-138</sup>. In combined therapy, LOLA, along with standard therapeutic options, has a positive impact on improving HE treatment outcomes<sup>139,140</sup>.

In meta-analyses and controlled studies, the effectiveness of both formulations has been proven, but due to the heterogeneity of studies, additional controlled studies on the effectiveness of oral therapy in OHE, parenteral therapy in CHE, therapy for HE in TIPS, and prophylactic use are needed<sup>122,124</sup>. Based on the results of controlled studies, the oral formulation of LOLA seems to be superior to the intravenous form in studies treating patients with CHE, either in psychometric test results or in preventing progression to OHE<sup>141</sup>. Although studies on the use of LOLA in primary or secondary prophylaxis of HE are not numerous, in published studies, the oral formulation of LOLA is significantly associated with a lower frequency of OHE episodes (RR 0.44) and a prolonged time until their occurrence (HR 0.431)<sup>136</sup>. It is important to note that the use of LOLA, compared to other therapeutic options, is associated with negligible side effects and interactions with other medications. The recommended daily dose of parenteral LOLA is 20-30 g, and oral LOLA is 3 times 3-6 g *per* day, with dose titration based on effectiveness assessment.

#### 6.4.5 Branched-chain amino acids (BCAA)

Branched-chain amino acids (BCAA) are recommended for use as concomitant or alternative therapy in patients who do not respond to standard treatment or cannot tolerate the intake of animal proteins to achieve nitrogen balance<sup>122</sup>. Oral administration of BCAA has a favorable effect on the recovery of hepatic encephalopathy (RR 0.73), with no effect on mortality, quality of life, nutritional status, and prophylaxis of recurrent HE<sup>142</sup>. In most studies, the recommended dose of BCAA is 0.25 mg/kg of ideal body weight. The use of BCAA is associated with a higher frequency of nausea and vomiting compared to placebo (RR 5.56), poor palatability, and higher treatment costs compared to conventional therapy

(which poses a challenge in positioning BCAA as first-line therapy).

#### 6.4.6 Liver transplantation

Patients with recurrent or persistent hepatic encephalopathy (HE) should be considered for liver transplantation, and the first episode of overt hepatic encephalopathy (OHE) should prompt referral to a transplant center for re-evaluation<sup>124</sup>. This is especially relevant for the treatment of recurrent or persistent HE in patients with spontaneous or surgically created portosystemic shunts or HE where motor dysfunction (hepatic myelopathy) predominates and is not caused by the effects of ammonia.

Due to the complexity of treating patients with HE and liver cirrhosis, it is essential to conduct treatment in specialized institutions with experience in managing these conditions. This includes regular monitoring, education on proper nutrition, prevention of precipitating factors, recognition of HE symptoms, adherence to treatment and prophylaxis for HE, and support in the family and socio-economic care of patients.

## 7 VASCULAR LIVER DISEASES

Vascular liver diseases are classified as rare conditions with a prevalence of 5/10,000<sup>143-145</sup>. Among them, portal vein thrombosis, Budd-Chiari syndrome, sinusoidal obstruction syndrome, and porto-sinusoidal vascular liver disease stand out in terms of prevalence and clinical significance, all of which are covered by these guidelines<sup>143</sup>.

### 7.1 Portal Vein Thrombosis

Portal vein thrombosis can be partial or complete, and acute or chronic, with different stages of the disease. In chronic thrombosis, numerous venous collaterals develop to bypass the site of obstruction, a condition referred to as portal cavernoma<sup>6,146</sup>. Portal vein thrombosis arises from a combination of local and systemic risk factors listed in Table 4. The most common local risk factor in non-cirrhotic patients is intra-abdominal inflammatory process and malignant disease, while in cirrhotic patients, it is slow flow through the portal vein, contributed to by portosystemic shunts, with other local factors further increasing the risk. Systemic factors include inherited thrombophilia and



Table 4. Systemic and local risk factors in portal vein thrombosis

	<b>Systemic risk factors</b>	<b>Local risk factors</b>
<b>Non-cirrhotic patients</b>	Myeloproliferative neoplasms	Intra-abdominal inflammatory process
	Antiphospholipid syndrome	Abdominal trauma
	Pregnancy, oral contraceptives	Abdominal surgeries
	Factor V Leiden mutation	Malignancy
	Paroxysmal nocturnal hemoglobinuria	
	Prothrombin G20210A gene mutation	
	Deficiency of protein C, protein S, antithrombin	
	Autoimmune diseases	
<b>Patients with advanced liver disease</b>	Decreased blood flow due to portal hypertension	Hepatocellular carcinoma
	Malignancy	Intra-abdominal surgeries
	Developed portosystemic collaterals	

acquired conditions that increase blood coagulability, such as myeloproliferative neoplasms (MPN) and the systemic inflammatory response<sup>143,147,148</sup>. Patients may present as asymptomatic or symptomatic with complications of portal hypertension<sup>148</sup>. If mesenteric veins are involved, the development of intestinal ischemia is possible<sup>149</sup>. The diagnosis of portal vein thrombosis is made using imaging methods such as color Doppler, computed tomography (CT), or magnetic resonance imaging (MRI) with contrast enhancement. Therapeutic approach varies depending on the presence of liver cirrhosis<sup>150</sup>.

### 7.1.1 Portal vein thrombosis in non-cirrhotic patients

The goal of treatment is recanalization and preventing the spread of thrombosis to avoid intestinal

ischemia. Additionally, it is necessary to treat the local cause of thrombosis if detected<sup>151</sup>. Anticoagulant therapy is applied for a minimum of 6 months from the onset of symptoms, or lifelong in the case of confirmed thrombophilia<sup>148,149</sup>. Treatment begins with low-molecular-weight heparin (2x1 mg/kg)<sup>151</sup> and continues with oral vitamin K antagonists or direct-acting oral anticoagulants (DOACs) if there are no contraindications. After 6 months, a contrast-enhanced abdominal CT is performed to assess the effectiveness of therapy. If recanalization has not occurred, further tests are needed to verify portal hypertension (PH) and its complications, including esophagogastroduodenoscopy (EGD) to confirm varices in the esophagus and stomach. In the case of PH, the same approach as in patients with cirrhosis and PH is applied<sup>147-149</sup>.

### 7.1.2 Portal vein thrombosis in patients with liver cirrhosis

In patients with liver cirrhosis, it is essential to assess the initiation of anticoagulant therapy, considering that spontaneous recanalization occurs in about 40% of cases, taking into account the risk of bleeding. All patients with cirrhosis and portal vein thrombosis are recommended to undergo EGD to verify varices in the esophagus or stomach, and depending on the findings, initiate therapy with non-selective beta-blockers (NSBB) or endoscopic variceal ligation<sup>152</sup>. Anticoagulant therapy is indicated in patients with cirrhosis and (a) recent (duration <6 months) complete or partially occlusive (occupying >50% of the lumen) portal vein thrombosis (PVT) with or without extension into the upper mesenteric vein, (b) symptomatic PVT regardless of extension, and (c) patients eligible for liver transplantation regardless of extension and degree of portal vein occlusion. If it is partial thrombosis (occupying <50% of the lumen of the portal vein trunk) and imaging methods show progression of thrombosis within a 3-month follow-up period, anticoagulant therapy is indicated<sup>147</sup>. Since the diagnosis of portal vein thrombosis in these patients is often incidental during routine ultrasound, the timing of starting anticoagulant therapy is crucial, where earlier initiation has shown better response and more frequent recanalization.

Treatment starts with low-molecular-weight heparin and continues with vitamin K antagonists. Treatment with DOACs is possible only in patients with compensated cirrhosis and eGFR >30 mL/min/1.73 m<sup>2</sup>, while it is contraindicated in those with advanced cirrhosis<sup>153</sup>. In patients with thrombosis of the portal vein trunk who do not achieve recanalization with anticoagulant therapy, especially if they are candidates for liver transplantation, TIPS placement is recommended.

## 7.2 Porto-Sinusoidal Vascular Disease

Porto-sinusoidal vascular disease (PSVD) is characterized by the absence of cirrhosis with the presence of certain histological signs characteristic of PSVD, such as obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal fibrosis, with or without portal hypertension (PH). This definition was adopted in 2019, replacing the previous

term Idiopathic Non-Cirrhotic Portal Hypertension, along with modifications to diagnostic criteria<sup>154,155</sup>. PSVD leads to presinusoidal PH, resulting in a normal or <10 mm Hg HVPG even in the presence of clear clinical signs of PH. Half of the patients have an associated disease (hematologic diseases, e.g., myeloproliferative disorders, thrombophilia, immune system diseases, genetic diseases, infections) or have been exposed to certain drugs (e.g., azathioprine, oxaliplatin) associated with the pathogenesis of PSVD<sup>155,156</sup>.

Porto-sinusoidal vascular disease should be suspected in patients with clinical signs of PH (e.g., esophageal varices, portosystemic collaterals on imaging) in the absence of chronic liver disease or with only mild liver lesions. In some patients, the liver may have a nodular appearance reminiscent of cirrhosis, with splenomegaly and thrombocytopenia, but biochemical parameters of liver function are normal, and liver stiffness is below the range of cirrhosis (usually <10 kPa), with elevated spleen stiffness. Some patients present with only a mild increase in liver enzymes (elevated in about 80% of patients with PSVD), without other imaging features of PSVD and without signs of PH, so the diagnosis can be made solely based on histological changes characteristic of PSVD<sup>156,157</sup>. Portal vein thrombosis develops in 30%-40% of patients with PSVD with a median of 5 years after diagnosis, so in case of unclear etiology of portal vein thrombosis, PSVD should be considered as an etiologic factor in the differential diagnosis<sup>158,159</sup>.

Patients usually have no symptoms until the onset of PH complications, with the main complications being variceal bleeding and portal vein thrombosis. Even 20%-40% of patients with PSVD initially present with bleeding from esophageal varices, while ascites and encephalopathy are less common<sup>158</sup>. According to current data, patients with PSVD do not have an increased risk of developing hepatocellular carcinoma (HCC), so screening is not recommended<sup>155,156</sup>. The treatment of PSVD is based on managing PH complications, primarily primary prophylaxis of variceal bleeding (using non-selective beta-blockers) and treating portal vein thrombosis<sup>155</sup>. Currently, there is not enough evidence to support the use of anticoagulant drugs in the prevention of portal vein thrombosis.

### 7.3 Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) refers to the obstruction of venous flow occurring anywhere from the right atrium to the small branches of the hepatic veins, including obstruction of the inferior vena cava and their combination, excluding cardiac causes and sinusoidal obstruction syndrome<sup>160,161</sup>. Flow obstruction leads to sinusoidal congestion, consequent hypoxia of the liver parenchyma, and hepatocellular necrosis<sup>143</sup>. Clinical presentation can vary from asymptomatic disease detected by imaging methods or abnormal biochemical findings, the presence of PH, to acute liver failure<sup>146,160,162</sup>. Primary BCS refers to changes in the liver veins themselves, such as thrombosis or phlebitis, while secondary BCS refers to the compression or invasion of veins from surrounding areas, such as malignant processes, cysts, abscesses, etc.<sup>146</sup>. Hematologic diseases, liver diseases, malignancies, and chronic use of contraceptives are among the most common causes of BCS<sup>146</sup>. BCS should be considered in all patients with acute or chronic liver diseases. Diagnosis is established through imaging methods, which can simultaneously rule out local causes of compression/invasion of the liver veins, and comprehensive screening for thrombophilia is necessary<sup>160</sup>.

In the treatment of BCS, it is important to identify the cause and then treat it specifically. The first-line treatment is anticoagulant therapy, initially using low-molecular-weight heparin (2x1 mg/kg body weight) for 5 to 10 days, followed by vitamin K antagonists or direct-acting oral anticoagulants (DOACs). Anticoagulant therapy is lifelong<sup>6,146,163</sup>. In case of treatment failure with anticoagulant therapy, angioplasty is applied if the stenosis is suitable for radiological intervention, with or without stent placement. In patients who do not respond to pharmacological treatment and are not candidates for angioplasty or stent placement, the method of choice is the placement of a transjugular intrahepatic portosystemic shunt (TIPS). In patients with acute liver failure, liver transplantation is the method of choice. Treatment of PH complications is the same as in the treatment of cirrhotic liver disease. Due to the increased risk, screening for hepatocellular carcinoma is recommended for BCS patients using a combination of abdominal ultrasound and AFP determination every 6 months<sup>164</sup>.

### 7.4 Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), formerly known as veno-occlusive disease, is characterized by damage to the vascular endothelium of the sinusoids, resulting in the obstruction of central veins and congestion of the liver, leading to a post-sinusoidal form of PH. It is mostly caused by drugs used in chemotherapy and some immunosuppressants<sup>143</sup>. Newer modalities of anticancer treatment and the use of prophylactic therapy have partially reduced the incidence of this syndrome. Clinical presentation varies from asymptomatic patients with elevated liver transaminases to the development of PH and multiorgan failure. The most common symptoms include weight gain due to ascites, hepatomegaly, and jaundice (Seattle and Baltimore criteria)<sup>165,166</sup>. The disease should be suspected in case of the development of these symptoms and signs in patients with recent exposure to anticancer or immunosuppressive drugs, especially after myeloablative chemotherapy used in preparation for bone marrow transplantation (most commonly allogeneic). Imaging methods can reveal hepatomegaly, gallbladder edema, ascites, and splenomegaly, with Doppler showing preserved flow in large hepatic veins and hepatofugal flow in the portal vein in individuals whose previous flow was in the correct direction. However, these signs are not present in all patients, so in such cases, liver biopsy and measurement of HVPG are needed for diagnosis<sup>166</sup>. As a prophylactic measure, the use of ursodeoxycholic acid at a dose of 12 mg/kg daily is recommended in all patients preparing for allogeneic bone marrow transplantation, and therapy should start the day before myeloablative chemotherapy and continue for 3 months after transplantation. Treatment of moderate to severe forms of SOS is carried out with defibrotide, which is the only approved therapy for this disease. Defibrotide is administered at a dose of 25 mg/kg/day for at least 21 days or until the clinical symptoms and signs of SOS disappear<sup>166</sup>.

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## Sažetak

## HRVATSKE SMJERNICE ZA DIJAGNOSTIKU I LIJEČENJE PORTALNE HIPERTENZIJE

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Bolesti jetre trenutno su jedanaesti vodeći uzrok globalne smrtnosti, a ciroza zauzima deveto mjesto među uzrocima smrti u Europi. Progresija ciroze dovodi do razvoja komplikacija poput portalne hipertenzije (PH), zatajenja jetre i hepatocelularnog karcinoma. PH igra ključnu ulogu u napredovanju kronične bolesti jetre i predstavlja neovisan prediktor smrtnosti kod osoba s cirozom. S obzirom na brojne novosti u klasifikaciji, dijagnozi i strategijama liječenja PH, usvajanje nacionalnih smjernica postalo je imperativ kako bi se poboljšala skrb za ovu skupinu bolesnika. U svjetlu Baveno VII. konsenzusa, kao i rezultata istraživanja objavljenih nakon njega, radna skupina Hrvatskoga gastroenterološkog društva izradila je smjernice koje su razmatrane i usuglašene tijekom 2023. godine. Ovdje predstavljamo sažetu verziju smjernica s ključnim preporukama.

*Ključne riječi: Portalna hipertenzija; Vaskularne bolesti jetre; Smjernice; Dijagnostika; Liječenje*