National Consensus on Portal Hypertension Management in Indonesia

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ABSTRACT

Portal hypertension is a clinical syndrome that consists of hypersplenism, ascites, gastroesophageal varices, and encephalopathy. This condition is marked by increased portal pressure gradient and may occur with or without liver cirrhosis. To date, portal hypertension remains as the leading cause of severe complications and death of a patient with chronic liver disease, especially liver cirrhosis. Therefore, thorough understanding about management of portal hypertension is strongly required, especially considering that many complications of portal hypertension require early diagnosis and treatment to improve the prognosis of the patients. Additionally, although hepatic venous pressure gradient (HVPG) measurement has become a gold standard procedure for measuring portal pressure in the last twenty years, utilization of this method in Indonesia has been hindered by reluctance of the patients due to its invasiveness, high cost, and limited availability. This consensus is developed with evidence-based medicine principles to provide a guideline for portal hypertension management for general practitioners, specialists, and consultants, to achieve better clinical outcomes of portal hypertension in Indonesia.

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

INTRODUCTION

Portal hypertension is a clinical syndrome that consists of hypersplenism, ascites, gastroesophageal varices, and encephalopathy. This condition is marked by increased portal pressure gradient in different levels of the portal vein system. Portal hypertension can occur with or without liver cirrhosis. In liver cirrhosis, structural changes in liver sinusoids, such as liver fibrosis and production of regenerative nodules, can increase intrahepatic resistance; thus, increasing the portal pressure. Increased production of nitric oxide (NO) in splanchnic circulation can also induce splanchnic vasodilatation. Eventually, splanchnic vasodilatation will increase portal blood flow,

causing worsened portal hypertension. As a result, there will be abnormal circulation in the form of hyperdynamic circulation, leading to other complications.[1,2]

To date, portal hypertension remains as the leading cause of severe complications and death in a patient with liver cirrhosis. Additionally, although in the last twenty years hepatic venous pressure gradient (HVPG) measurement has become a gold standard procedure for measuring portal pressure, utilization of this method has been hindered by its invasiveness and limited availability, especially in less specialized medical centers. Therefore, this consensus is developed to provide a guideline for portal hypertension management for general practitioners, specialists, and consultants, to achieve better clinical outcomes of portal hypertension in Indonesia.

EPIDEMIOLOGY

Chronic liver disease has affected approximately 300 million people around the world. Globally, the incidence and prevalence of liver cirrhosis are still increasing every year. In Indonesia, ten healthcare centers reported that more than 1,500 patients were diagnosed with liver cirrhosis in 2020. Unfortunately, gastrointestinal endoscopic examination was performed only in a small portion of the patients (35.5% patients with liver cirrhosis) (**Figure 1**).[3] Liver cirrhosis is also the fourth most common cause of death due to non-communicable diseases. The death rate caused by liver cirrhosis has increased up to 65% in the last 17 years.[4] A cumulative data in Cipto Mangunkusumo National General Hospital showed that patients with liver cirrhosis are dominated by male gender (77%) and Child-Pugh A category (51%). Other reports demonstrated an increase in death caused by liver cirrhosis and hepatocellular carcinoma, which is estimated to be 50 million deaths annually in the last two decades.[3,5]

CLASSIFICATION

As mentioned above, HVPG measurement is currently the gold standard to evaluate portal pressure, as well as the best indirect method to assess portal vein pressure. HVPG is defined as the pressure gradient between portal vein and inferior vena cava. The normal range of HVPG is 3-5 mmHg. Diagnosis of portal hypertension can be determined if HVPG is higher than 5 mmHg.[1,2]

Mild Portal Hypertension

In general, patients with compensated liver cirrhosis usually do not show any symptoms.

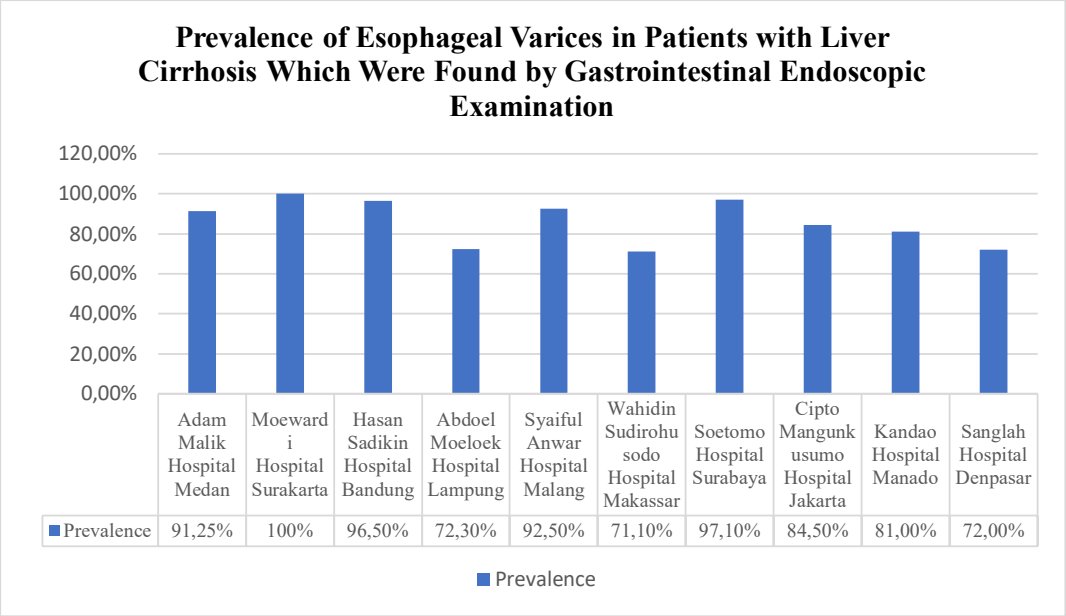

Figure 1. Prevalence of esophageal varices (%) in patients with liver cirrhosis diagnosed with gastrointestinal endoscopic examination in Indonesia (2020).

Compensated liver cirrhosis itself can be differentiated into mild portal hypertension and clinically significant portal hypertension (CSPH).[1,6] Mild portal hypertension is diagnosed when HVPG is within the range of 6-9 mmHg. The therapeutic goal is to prevent the progressivity into CSPH.[6,7]

Clinically Significant Portal Hypertension (CSPH)

CSPH is diagnosed when HVPG is ≥ 10 mmHg. Increase of portal pressure by more than 10 mmHg will contribute to the progression of liver cirrhosis into more advanced stages. Patients with CSPH can be present with or without complications. The therapeutic goal in patients with or without complications is to prevent any decompensation events, especially gastroesophageal variceal bleeding.[6,7]

Clinical Stages of Portal Hypertension

Clinical stages and manifestation of portal hypertension depend on the presence of decompensation, as well as the presence of esophageal varices and other complications of portal hypertension in liver cirrhotic condition. Therefore, the therapeutic goal needs to be adjusted with the clinical stages (**Table 1**).[6,7] A study conducted by Procopet, et al.[8] also highlighted the association between HVPG measurement and clinical outcomes in patients with portal hypertension (**Table 2**).

Table 1. Stages, clinical manifestation, and therapeutic goal of portal hypertension in patients with compensated and decompensated liver cirrhosis.[6,7]

Stages	Compensated Liver Cirrhosis			Decompensated Liver Cirrhosis		
HVPG (mmHg)	< 10	> 10		> 12		
Varices	No	No	Yes	Yes		
Portal Hypertension Complications	No	No	No	Acute variceal bleeding	History of variceal bleeding without other complications	History of variceal bleeding with other complications
Therapeutic Goal	Prevent the CSPH	Prevent the decompensated condition	Prevent the decompensated condition (the first episode of bleeding)	Bleeding control, early prevention of bleeding recurrence and mortality	Prevent the progressivity of decompensated condition (the continuous bleeding) and other complications	Prevent the progressivity of decompensated condition and mortality or other complications

Table 2. Association between portal pressure measurement and clinical outcomes in patients with portal hypertension.[8]

HPVG (mmHg)	Clinical Outcomes
< 5	Normal
6-9	Mild portal hypertension
>6	Progressivity of chronic viral hepatitis, high risk of recurrence after liver transplantation
10	Clinically significant portal hypertension (CSPH)
>10	Progression into esophageal varices, ascites, decompensation, advanced hepatocyte abnormalities, decompensation after liver resection
>12	Esophageal varices bleeding
>16	High mortality
> 20	Failure to bleeding control
> 22	High mortality in severe alcoholic hepatitis

PATHOGENESIS

As time goes by, production and accumulation of extracellular fibrosis in the liver, which were caused by chronic liver injury, can also induce septal fibrosis progressively. Consequently, septal fibrosis will inhibit oxygenation and blood diffusion in the liver parenchyma. The final stage of liver destruction is marked by the significant distortion of the anatomical structure of the liver, such as diminished normal hepatocytes, microvascular and macrovascular changes, neovascularization, formation of nodules, and portosystemic shunt.[1] Another main characteristic of chronic liver disease is a long asymptomatic period. In the first phase (compensated cirrhosis), the patient may show no sign or only minimal symptoms. In that period, portal hypertension occurs minimally in line with decreased liver function. Portal hypertension is a critical process of the transition from compensated cirrhosis into the decompensated state, which is also marked by clinical complications, such as ascites, acute variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and hepatic encephalopathy.[3,5]

Portal pressure is mainly influenced by vascular resistance and portal venous system blood flow (**Figure 2**).[9] Increased portal pressure is caused by increased intrahepatic resistance and portal blood flow.[10] The increase of intrahepatic resistance is caused by mechanical (structural distortion of liver parenchyma) and functional (an increase of intrahepatic vascular tone caused by the reduced vasodilatation and imbalance between vasoconstrictor and vasodilator) factors. There are two different mechanisms associated with NO production which may cause increased portal blood flow. The increase of NO production will induce splanchnic vasodilatation, leading to increased portal blood flow. Higher concentration of NO can also induce vasodilatation in systemic circulation, causing arteriole hypotension and relative renal hypoperfusion. Both conditions can stimulate the activation of the renin-angiotensin-aldosterone system (RAAS), promote fluid and sodium retention, cause blood augmentation, and increase cardiac output. As a result, blood flow into the portal system will be increased, and portal pressure will also increase.[11]

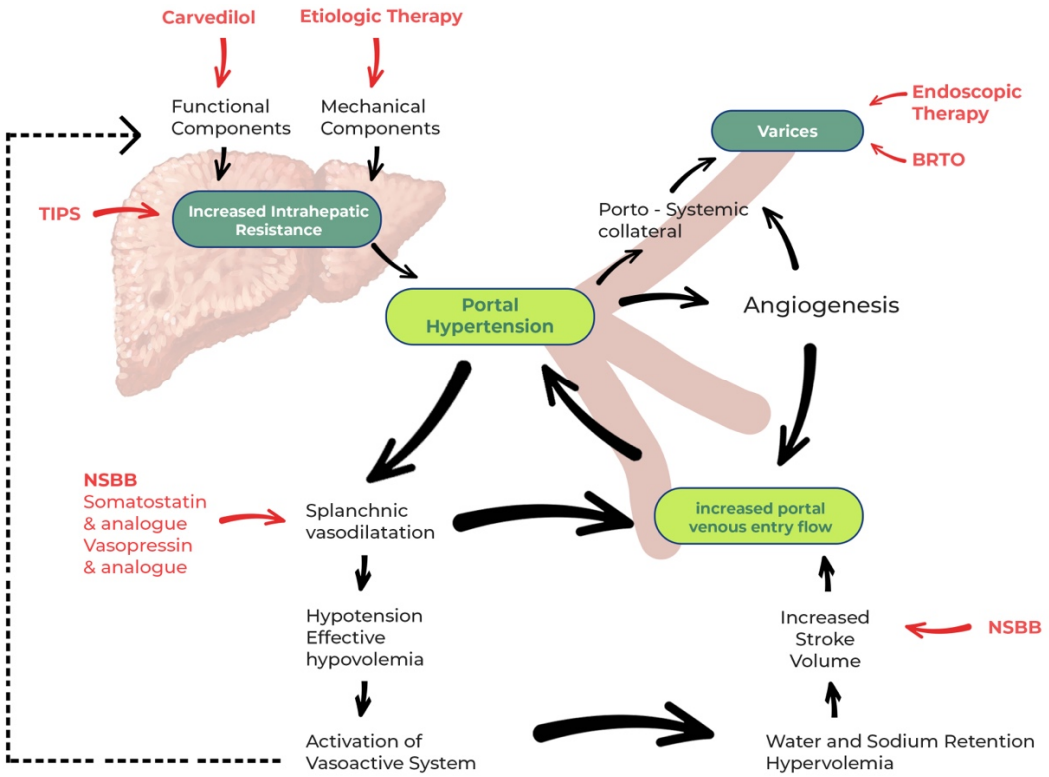

Figure 2. Pathophysiology of portal hypertension (Adapted from [10]).

Increased portal pressure will signal the splanchnic system to induce vasodilatation, and thus, leading to increased blood flow into the portal system. A factor associated with this condition is production of local vasoactive substances by vascular endothelium (NO, prostacyclin, carbon monoxide). The angiogenesis mechanism is stimulated by vascular endothelial growth factors (VEGF) and platelet-derived growth factors (PDGF). NO also plays an important role to induce the splanchnic vasodilatation and angiogenesis process. The concentration of NO in hepatic circulation will be decreased, but it will be increased in the splanchnic area.[10,11]

Portal hypertension also stimulates the production of portosystemic collateral vascular as a response to the increase of portal pressure. Changes of portal pressure is detected by intestinal microvascular cushion and artery from splanchnic circulation. The microvascular cushion will then produce several angiogenic factors, such as VEGF and placental growth factors (PlGF), which will stimulate the formation of portosystemic collateral vessels. The formation of collateral vessel or angiogenesis is an important process to form esophageal varices and ascites.[10,12] Portal hypertension also induces hyperdynamic circulation through the β-adrenergic system as a response towards systemic hypotension.[10] This condition is marked by reduced mean arterial pressure (MAP), reduced systemic vascular resistance (SVR), and elevated cardiac index (CI).[12,13]

DIAGNOSIS

There are several methods to measure portal vein pressure, and currently, hepatic vein catheterization is considered as the best method. The difference between wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) is called HVPG. Therefore, HVPG describes a pressure gradient between portal vein and inferior vena cava.[6,7,14] A study reported that HVPG > 10 mmHg is an independent indicator for varices,[14] decompensation (variceal bleeding, ascites, encephalopathy),[15] increased hepatocellular carcinoma incidences (up to 6-folds increase), and worsened conditions after liver resection.[16] In compensated CSPH, the value of HVPG > 16 mmHg is a prognostic factor for clinical decompensation.[17] In acute variceal bleeding, the value of HVPG > 20 mmHg is also a prognostic factor of recurrent bleeding, therapeutic failure, and higher mortality.[18]

Non-Invasive Examination

Clinical Examination

Clinical examination of portal hypertension consists of physical examination, laboratory examination, imaging studies, liver stiffness measurement, and spleen stiffness measurement. Spider nevi or abdominal portosystemic collateral signs can be found in patients with portal hypertension through physical examination. Other common clinical findings are splenomegaly and ascites.[6]

Biomarker Examination

One of the most common laboratory findings in portal hypertension is thrombocytopenia. Thrombocytopenia is associated with HVPG and gastroesophageal varices, but it is not accurate in diagnosing and excluding portal hypertension or gastroesophageal varices.[18]

Several biomarkers have been evaluated for diagnosing CSPH or severe portal hypertension (**Table 3**). However, most studies were conducted with small sample size, with history of alcohol consumption as the most common etiology of chronic liver disease. In addition, not all serum biomarker examinations are available widely. In conclusion, further validation studies are still needed before these biomarkers can be applied in daily clinical practices.

Other examinations to measure portal hypertension with non-invasive methods are AST to Platelet Ratio Index (APRI) score and Fibrosis-4 (FIB-4) index. APRI can be used as a value or index of reference to predict severe esophageal varices. The measurement of APRI and FIB-4 are recommended by World Health Organization (WHO) to assess the degree of liver fibrosis.[27]

Table 3. Summary of studies which evaluated serum biomarkers for portal hypertension examination in liver cirrhotic patients.

No.	Authors	Biomarkers	Etiology	Results
1.	Busk, et al. (2014)[19]	Tissue inhibitor metalloproteinase -1 (TIMP-1)	n = 84 (dominantly caused by alcohol consumption)	TIMP-1 is significantly correlated with HVPG (r = 0.40; p < 0,0001) For HVPG ≥ 12 mmHg Threshold value: 173.9 ng/mL with sensitivity 99%, specificity 49%, NPV 86%, PPV 88% Cut-off: 33.6 ng/mL, sensitivity 57%, specificity 93%, NPV 33%, PPV 98%
2.	Sandahl, et al. (2015)[20]	CD163-fibrosis portal hypertension score -0.05xsCD163 (mg/L) + 0.03xP3NP (mg/L) + 0.021x HA (mg/L) + 0.001xTIMP-1 (mg/L)	Estimation cohort = 80 Alcohol = 31 Viral = 41 Others = 8 Validation Cohort = 80 Alcohol = 63 Others = 14	For CSPH detection (HVPG > 10 mmHg): Cohort estimation Threshold value: 1.4; sensitivity 100%, specificity 25%, PPV 93%, NPV 100% Threshold value: 3.6; sensitivity 70%, specificity 88%, PPV 99%, NPV 27% Validation cohort Threshold value: 1.4; sensitivity 98%, specificity 50%, PPV 89%, NPV 94% Threshold value: 3.5; sensitivity 92%, specificity 69%, PPV 93%, NPV 73%
3.	Leeming, et al. (2015)[21]	Type IV Collagen (Pro C5)	n = 94 Alcohol consumption	Correlation coefficient between Pro-C5 and HVPG: r = 0.33, p < 0.01 For CSPH Detection: Threshold value: 330 ng/mL; sensitivity 79.7%, specificity 64%, PLR+: 2.2; NLR: 0.32; AUC: 0.73 For detection of HVPG > 16 mmHg vs 10-16 mmHg: Threshold value: 346 ng/mL; sensitivity 80.5%; specificity 48.3%; PLR 1.6; NLR 0.4; AUC: 0.68
4.	Hametner, et al (2016)[22]	VITRO Score (Von Willebrand Factor Antigen/ Thrombocyte Ratio)	n=236 Alcoholism = 93 Hepatitis C = 67 NASH = 29 Others = 19 Unknown = 28	For CSPH detection: Threshold value > 1.58; AUC: 0.86 (95% CI 0.81-0.91); sensitivity 80%, specificity 70%, PPV 93.2%, NPV 40.1%
5.	Bruha, et al. (2016)[23]	Osteopontin	n =154 Alcoholism = 112 Viral = 112 Others included NASH = 20	Correlation between osteopontin and HVPG, p = 0.002, r = 0.25 For detection of HVPG > 10 mmHg: Threshold value: 80 ng/mL; sensitivity 75%, specificity 63%, PPV 92%, NPV 31%; AUC 0.763 For detection HVPG > 12 mmHg: Threshold value 90 ng/mL; sensitivity 71%, specificity 62%, AUC 0.725
6.	Lim, et al. (2016)[24]	Serum Apelin	n = 215 Alcoholism = 155 HBV = 36 HCV = 3 Alcoholism and HBV infection = 12 Alcoholism and HCV infection = 2 Cryptogenic = 7	Association between s-apelin and HVPG (R^2 = 0.356, p < 0.001) AUC for prediction of CSPH: 0.962 Mean of s-apelin concentration in CSPH vs non-CSPH: 946.3±155.0 pg/mL vs 550.9±126.6 pg/mL, p < 0.001

7.	Kirnake, et al. (2018)[25]	APRI	n= 277	Correlation between APRI and HVPG (Spearman's rho = 0.450, p < 0.001)
			Alcoholism=135	For detecting HVPG > 12 mmHg.
			Cryptogenic/NASH = 104	Threshold value: 0.876; sensitivity 71% (95% CI 65-77%), specificity 78% (95% CI 65-89%), PPV 94% (95% CI 90-96%), NPV 38% (95% CI 32-44%), AUC 73% (95% CI 67-78%)
			Hepatitis B = 8	
			Hepatitis C = 23	
			Hepatitis B and C = 3	
8.	Zou, et al. (2019)[26]	von Willebrand Factor (vWF)	Meta-analysis from six studies (n=994)	
			Alcohol (282), viral (260), others etiologic (N/A)	For HVPG > 10 mmHg: pooled sensitivity 82% (95% CI 78-86%); specificity 76% (95% CI 68-83%); PLR: 3.11 (95% CI 1.99-4.86); NLR: 0.21 (95% CI 2.49-4.72); NLR: 0.21 (95% CI 0.11-0.40); AUC: 0.87 (95% CI 0.80-0.94)
				For HVPG > 12 mmHg: pooled sensitivity 86% (95% CI 80-90%); specificity 75% (95% CI 66-83%); PLR: 3.43 (95% CI 2.49-4.72); NLR: 0.19 (95% CI 0.14-0.27)

Equation (1):

$$\text{APRI} = \frac{\text{AST (upper limit normal)}}{\text{Thrombocyte Count}} \text{ x } 100 \text{ x } 10^9 \text{ L}$$

Equation (2):

$$\text{FIB} - 4 = \frac{\text{Age (Year)}}{\text{Thrombocyte Count x } \sqrt{ALT}} \text{ x AST}$$

A study by Kirnake V, et al. on 277 patients with liver cirrhosis shows a significant correlation between APRI and HVPG. The cut-off of APRI is 0.876, and this cut-off has a tremendous positive predictive value (PPV) as high as 94% to predict HVPG > 12 mmHg with moderate accuracy (73%). APRI can be used as a predictor for severe esophageal varices. The value of APRI > 1.4 demonstrated sensitivity of 93.9% and specificity of 60% as a reference of index value for early intervention in patients with severe esophageal varices.[25] Cho EJ, et al. reported the accuracy of several biomarkers for assessing CSPH and esophageal varices in patients with liver cirrhosis caused by alcohol consumption. In their study, FIB-4 with cut-off 4.1 to detect CSPH had sensitivity of 70%, specificity of 42.3%, PPV of 13.5%, and NPV 59.2% with area under the curve (AUC): 0.65 (95% CI: 0.5-0.8).[28] This study showed that FIB-4 had low accuracy for assessing CSPH or even esophageal varices. The limitation of APRI and FIB-4 is the value of these diagnostic modalities is dominantly influenced by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by the degree of inflammation, such as in acute hepatitis or acute on chronic liver failure (ACLF).[27] Due to its low sensitivity, specificity, and positive predictive value compared to endoscopic examination, APRI is not recommended as an alternative examination for esophageal varices screening.[29]

Imaging Modalities

Several imaging modalities can be used to diagnose and evaluate portal hypertension, such as abdominal ultrasonography (Abdominal US), magnetic resonance imaging (MRI), computed tomography (CT-scan), and transient elastography.[30]

- **Abdominal US**
  Abdominal US is a non-invasive examination for patients with chronic liver disease and liver cirrhosis. Abdominal US is considered as a more cost-effective method with less adverse events in comparison to CT-scan and abdominal MRI to assess portal hypertension and liver fibrosis. Abnormal

findings that support the diagnosis of CSPH are the signs of liver cirrhosis, splenomegaly, ascites, portal vein dilatation, splenic vein or mesenteric vein dilatation, portosystemic collateral (recanalization of the paraumbilical vein, spontaneous splenorenal circulation, and the dilatation of gastric vein), venous return of portal vein, and reduced velocity of hepatofugal portal venous blood flow.[29] Abdominal US can also be used for blood flow identification in hepatic artery, hepatic vein, and portal vein. An example of abdominal US image with M-mode in the spleen of patients with portal hypertension is attached below. The figure also shows prominent varices at the posterior side of the spleen (**Figure 3**).[31] Hepatic vein blood flow wave can be used as a predictor to assess the severity of portal hypertension because of its clinical association with HVPG. Nevertheless, abdominal US also has several limitations, such as operator-dependent, variability between intra- or even interobserver, influence of inspiration and expiration towards the results, as well as the presence of gas, ascites, and obese condition which may also influence the validity of the results.[29]

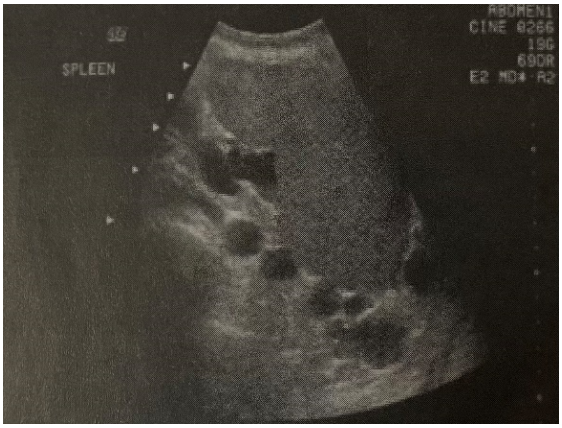

Figure 3. Abdominal ultrasound image of a patient with portal hypertension.[31]

Several parameters of Doppler US that are used as diagnostic parameters are blood flow velocity, flow direction, damping index, intraparenchymal splenic artery resistance index (SA-RI), superior mesenteric artery-pulsatility index (SMA-PI), and right interlobar renal artery resistive index (RRA-RI)[31] (**Table 4**).

- MRI and CT-scan
  These modalities can be used as a standard method for diagnosing hepatocellular carcinoma in patients with liver disease,

Table 4. Summary of studies which evaluated diagnostic performance of Doppler parameters in portal hypertension.

Study	Number of Subjects	Etiology	Parameters	Cut-Off	Diagnosis	Se/Sp/PPV/NPV	AUROC
Kondo, et al.[32]	236	Mixed	Blood flow velocity	12.8 cm/s	Decompensation	68/75/68/75	0.73895
			Flow direction	Hepato-fugal	Prognosis	21.8/99.3/70.6/60.6	-
Kim, et al.[33]	76	Mixed	Damping index	0.6	Severe portal hypertension (HVPG > 12 mmHg)	75.9/81.8/91.1/58.1	0.860
Vizzutti, et al.[34]	66	Hepatitis C Viral	SA-RI	0.6	Severe Portal Hypertension	84.6/70.4/80/76	0.82
			SMA-PI	2.7	Severe Portal Hypertension	85.7/65.2/79/75	0.78
			RRA-RI	0.65	Severe Portal Hypertension	79.5/59.3/74/66	0.78

including liver cirrhosis. However, the accuracy of CT-scan and MRI in diagnosing early stages of liver cirrhosis are limited. However, MRI and CT-scan can still be used if complications, such as ascites and portal vein dilatation, occur. MRI and CT-scan are also considered as the best diagnostic modalities to find morphological changes in hepatic and adjacent tissues. Both modalities can also detect hemodynamic changes. With multidetector CT, the scanning process can achieve submillimeter size, and thus, enabling the device to assess portosystemic collateral condition. The sensitivity and specificity of both modalities are 93% and 80%, respectively, for detecting esophageal varices. Another application of CT-scan is esophagography CT multidetector. Esophagography needs air insufflation into the esophagus via an oral tube and patient is requested to ingest a capsule. Hitherto, these supporting examinations are still considered as safe and reliable. Therefore, these methods can be used as alternative examinations, especially for patients with contraindications to esophagogastroduodenoscopy.[35]

- **Magnetic Resonance Elastography (MRE)**
  MRE is a method to assess liver elasticity quantitatively. MRE can distinguish different body tissues with higher accuracy compared to other modalities, such as abdominal US, CT-scan, and conventional MRI. Another advantage in using this modality is lack of influence of body composition, lack of influence of the ability of operator, and the ability to assess liver function more thoroughly. Nonetheless, MRE is still considered as an expensive modality, and thus, making it less available for routine diagnostic modality.[29]
- **Transient Elastography**
  According to recent studies, progressivity of liver fibrosis is associated with increased liver stiffness. Transient elastography (Fibroscan) is the most common method for assessing liver stiffness.[30] Liver stiffness showed good correlation with HVPG (r= 0.55-0.86; $p < 0.04$), and hence, making it also possible to detect CSPH. The Baveno VI consensus recommended cut-off value of > 21 kPa to suspect CSPH in patients with compensated advanced liver disease caused by viral infection.[30,35] In line with progression of portal hypertension, there will also be a progressive increase in spleen size due to venous return to the spleen, hyperplasia, angiogenesis, and fibrogenesis.[30] In another study, spleen stiffness also showed good correlation with the findings of transient elastography and HVPG (r=0.78; $p < 0.05$). A study in patients with liver cirrhosis caused by hepatitis C infection demonstrated threshold value of liver stiffness < 40 kPa to exclude the probability of CSPH. This value had sensitivity as high as 98%. Moreover, threshold value of ≥ 53 kPa to suspect CSPH had specificity of 97%.[36] However, measurement of spleen stiffness with transient elastography also showed failure rate as high as 15-20%.[1]

Invasive Examination

HVPG Measurement

Measurement of HPVG is considered as the gold standard examination for portal hypertension. HVPG is the difference between WHVP and FHVP (**Table 5**). WHVP is measured by occluding hepatic vein until blood flow stopped and stasis occurred. Hepatic vein occlusion can be performed through distention of hepatic veins with a balloon catheter, while non distended balloon catheter can be used for measuring free hepatic venous pressure (non-occlusion). In patients with liver cirrhosis, HVPG is also a predictor of survival and risk of decompensation. Meanwhile, in decompensated patients, HVPG can be used to assess the risk of mortality. Furthermore, HVPG measurement can also be used as an indicator of prognosis and therapeutic efficacy in patients with portal hypertension, for instance, in the usage of propranolol.[24]

Continuous monitoring of HVPG changes should be performed due to its association with

clinical outcomes of the patients. Previous studies indicated that if HVPG value could drop for more than 20% from baseline value or decrease until it reaches < 12 mmHg, then the risk of rebleeding, ascites, encephalopathy, and death will also decrease significantly. In compensated liver cirrhosis, > 10% decrease in HVPG from baseline reduces the risk of esophageal varices, variceal bleeding, and death.[37] However, to date, non-invasive examination with decent accuracy in diagnosing changes of HVPG is still not available yet. A retrospective study by Choi SY, et al. in 23 liver cirrhosis patients with serial HVPG measurement showed that changes in liver stiffness level measured with shear-wave elastography correlated with HVPG changes. However, further studies with larger sample size are still necessary to validate the benefit of monitoring HVPG with liver elastography.[38] More data are also required to support the validity and applicability of HVPG monitoring in patients who receive primary prophylaxis.[39]

Esophagogastroduodenoscopy (EGD)

EGD is a standard procedure to diagnose gastroesophageal varices. EGD has also been demonstrated to be useful in predicting bleeding risk. Location, size, and characteristics of esophageal varices can be assessed with EGD (**Table 5**). However, there are still several concerns on the use of EGD due to its invasiveness, high cost, and complications, such as infection, bleeding and perforation.[6,36]

EGD screening is recommended for all liver cirrhotic patients at the time when diagnosis of cirrhosis has been established. After endoscopic screening, patients with moderate or large varicose veins should be treated to prevent bleeding episodes, while other patients, who do not have any history of prior esophageal varices and who have not received any therapy for the etiology of their liver cirrhosis, have to undergo periodical surveillance endoscopic examinations every two years. Meanwhile, patients, who have received therapy for the etiology of their liver cirrhosis, are recommended to have the surveillance every three years. If the initial screening reveals small esophageal varices, it is recommended to repeat the endoscopy one year afterwards if no etiologic therapy has been given or after two years if etiologic therapy has been given. If the patient shows any clinical signs of decompensation, it is advisable to perform EGD examination again.[6]

Liver Biopsy

Liver biopsy is a gold standard examination for diagnosing liver cirrhosis. Liver biopsy is usually followed by evaluation with scoring system to determine the degree and stages of chronic liver disease. However, this examination is invasive, thus the usage is limited. The risk of error in tissue sampling may also affect the results of examination (**Table 5**).[35]

Table 5. Summary of non-invasive and invasive diagnostic modalities for patients with portal hypertension in liver cirrhosis.[40]

Diagnostic Methods	Findings
Non-Invasive	
Ultrasonography (USG)	
Liver	Irregular surface, inhomogeneous, focal lesion in liver
Portal Vein	Dilatation, thrombosis +/-
Spleen	Splenomegaly
Portosystemic Collaterals, ascites	+
CEUS (Contrast-Enhanced Ultrasound) Examination	Slow enhancement of periportal/heterogeneous/ homogenous
Cross-sectional imaging	Better characterization of liver focal lesion
Elastography	
Liver Stiffness	↑
Spleen Stiffness	↑
Invasive	
Liver Biopsy	Fibrosis and changes in liver architecture
Liver Hemodynamic	Normal FHVP, WHVP↑, HVPG↑, hyperdynamic circulation
Endoscopy	Esophageal varices and hypertensive gastropathy are more commonly observed, whereas gastric varices are less common to be found

MANAGEMENT

Effective reduction of portal pressure can reduce the incidence of complications and improve survival in patients with cirrhosis. Therapeutic efficacy on portal pressure can be assessed indirectly through clinical outcomes, such as the incidence of variceal bleeding, or directly through HVPG assessment. Achieving a pressure gradient of less than 12 mmHg or a 20% decrease from baseline is associated with decreased incidence of significant complications.[11]

Ascites

The presence of ascites is one of the poor prognostic markers in cirrhotic patients, with a reduction in 5-year survival from 80% in compensated cirrhotic patients to 30% in decompensated cirrhotic patients with ascites. The main pathophysiology of ascites is sodium retention by the kidneys due to activation of the sodium retention system, such as RAAS and sympathetic nervous system. Decreased effective volume due to vasodilation of splanchnic arteries can lead to a positive fluid balance, causing an increase in extracellular fluid volume.[5] Ascites is classified according to the amount of fluid in the abdominal cavity (**Table 6**).[1,41] Diagnostic paracentesis is indicated in all patients with episodes of first, second, or third grade of ascites, as well as in all patients who require treatment for complications of cirrhosis. Assessment of neutrophil levels, total protein, albumin concentration, and fluid cultures should be performed. Cultures with at least 10 mL of ascites fluid were performed to exclude the possibility of bacterial peritonitis. In cases where the cause of ascites is unclear, serum ascites albumin gradient (SAAG) calculation can be helpful where SAAG > 1.1 g/dL indicates the involvement of portal hypertension in ascites formation.[5]

Ascites without Complications

Ascites without complications is defined as ascites without infection or refractory episodes or HRS. Generally, the management of ascites consists of sodium restriction, administration of diuretics, and therapeutic paracentesis. Sodium intake is maintained between 80-120 mmol/day, which is equivalent to 4.6-6.9 grams of salt/day. A diet with very low sodium intake (<40 mmol/day) should be avoided because it can cause complications when administered together with diuretics and interfere with the nutritional status of the patient. Fluid restriction is only recommended in hypervolemic hyponatremic patients with sodium levels <130 mEq/L with ascites and/or edema.[5,42]

Meanwhile, the goal of diuretic administration is to achieve a negative fluid balance, which can be shown from the weight loss. The effectiveness of diuretic administration in controlling ascites is about 90% in patients without renal impairment.[42] Ideally, weight loss must not exceed 500 mg/day in patients without peripheral edema and must not exceed 1000 mg/day in patients with peripheral edema to avoid contractions in plasma volume, which may lead to renal failure or hyponatremia.[43] In cirrhotic patients, secondary hyperaldosteronism plays a major role in sodium retention. Hence, drugs that work as anti-mineralocorticoids become drugs of choice for ascites. The maximum recommended dose is 400 mg/day. Related with delayed anti-mineralocorticoid effects, the dose of these drugs should not be increased in less than 72 hours.[5] On the other hand, in patients with long-standing ascites, sodium reabsorption in the proximal

Table 6. Management of ascites according to the severity grading.[5]

Classification	Definition	Management
1st Grade (mild ascites)	Ascites is only detected through ultrasonography examination.	No special treatment is required.
2nd Grade (moderate ascites)	Ascites appears as symmetric abdominal distension.	Sodium restriction and diuretic administration.
3rd Grade (severe ascites)	Ascites appears as a significant abdominal distention.	Large volume paracentesis and administration of albumin (8 gram/L of ascitic fluid that is removed through paracentesis) followed by sodium restriction and diuretic administration

tubule may occur. Therefore, in this group of patients, strong diuretics (loop diuretics) can be given. Furosemide can be administered as an adjunctive therapy by increasing the dose gradually (starting at 40 mg/day up to 160 mg/day – increased by 40 mg). In patients with good compliance, but ascites is still not controlled, the dosage of diuretic can be increased by doubling the dose (1:1 ratio) until it achieves the maximum dose of spironolactone (400 mg/day) and furosemide (160 mg/day). Once ascites mobilization is achieved, the dose of diuretic should be reduced gradually to the lowest dose needed to control ascites in order to minimize side effects.[42] The side effects that need to be noticed are fluid and electrolyte imbalances, such as hyponatremia, dehydration, renal impairment, hyperkalemia or hypokalemia, and subsequently, hepatic encephalopathy. Spironolactone also tends to cause gynecomastia and muscle cramps in some patients. [5,42]

In patients with large or grade 3 ascites, the first line of treatment is large-volume paracentesis (LVP) (more than 5 liters) performed in a single session. It is recommended to perform LVP with ultrasound guidance to reduce the possibility of side effects. Taking ascites fluid in large volume can potentially cause post-paracentesis circulatory dysfunction (PPCD). The clinical manifestations can be renal failure, dilutional hyponatremia, and hepatic encephalopathy. For this reason, plasma volume expansion at the end of the paracentesis is necessary. Administration of plasma expanders, such as dextran-70 (8 g/L of ascitic fluid taken), polygeline (150 ml/L), and saline (170 ml/L), has demonstrated similar efficacy to 20% albumin (8 g/L) if the fluid taken is less than five liters.[42]

Refractory Ascites

Refractory ascites is defined as ascites which cannot be mobilized or recurrent in a short duration after LVP or without any adequate response towards pharmacological treatment (**Table 7**). Refractory ascites is also one of the bad prognostic markers in cirrhotic patients, indicated by approximately 6-months of mean survival duration. Another term, i.e., recurrent ascites, is defined as the presence of recurrent ascites episodes for at least three times in one year.[5,42] Therapeutic LVP is considered as a safe and effective option for refractory ascites. It is recommended to stop diuretic administration when diagnosis of refractory ascites has been determined. Diuretic administration can be considered again if it can be tolerated by the patient with renal sodium excretion > 30 mmol/day.[42]

Aside from LVP, several other therapeutic options can be considered in managing refractory ascites. The first option is by creating Transjugular Intrahepatic Portosystemic Shunt (TIPS), where intrahepatic stent will be placed between hepatic vein and portal vein for portal decompression and for stimulating peripheral artery vasodilatation in short time.[42] The most common complication of TIPS is hepatic encephalopathy, especially with the use of bare stent graft.[44,45] The rate of complications decreased by 18% with the use of polytetrafluoroethylene-covered stent.[46] In general, TIPS is not recommended in the presence of serum bilirubin level higher than 3 mg/dL, platelet counts < 75,000, hepatic encephalopathy grade ≥ 2 or chronic, active infection, progressive renal dysfunction, severe systolic or diastolic dysfunction, or pulmonal hypertension.[5] The use of continuous drainage catheter can be considered if TIPS cannot be performed. Peritoneal catheter can be placed percutaneously by using tunnel or non-tunnel technique, depends on the types of catheters. It is important to remember that the use of catheter for more than 12 weeks has been associated with significantly higher risk of infection.[47,48] Hitherto, additional administration of alpha-adrenergic agonists, such as midodrine or clonidine, has not been recommended as a therapeutic option for refractory ascites.[5,42]

Hepatic Hydrothorax

Hepatic hydrothorax is defined as accumulation of transudate fluid inside the pleural cavity (usually more than 500 mL) in decompensated cirrhotic patients without any other cardiopulmonary comorbidities or pleural abnormalities.[49,50] The presence of intrathoracic negative pressure and intraabdominal positive pressure may lead to ascitic fluid movement through diaphragm minor openings. These openings are usually located on the tendinous

Table 7. Definition and diagnostic criteria of refractory ascites.[5]

Definition	
Diuretic-resistant ascites	Ascites which cannot be mobilized or recurrent ascites in short duration and cannot be prevented due to inadequate responses with sodium restriction and diuretic administration.
Diuretic-intractable ascites	Ascites which cannot be mobilized or recurrent ascites in short duration and cannot be prevented to avoid diuretic complications, and thus, leading to inability to achieve the most effective dose of diuretic.
Diagnostic Criteria	
Duration of therapy	When the patient has already been in intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least one week and sodium restriction (< 90 mmol/day).
Inadequate response	Mean weight loss < 800 gram after four days and lower urinary sodium excretion compared to sodium intake.
Early recurrence	Re-appearance of grade 2 or 3 ascites within 4 weeks after early mobilization.
Diuretic complications	- Hepatic encephalopathy caused by diuretics (excluding other possible causes). - Renal dysfunction caused by diuretics: increased serum creatinine for > 100% until > 2 mg/dL (177 umol/L). - Hyponatremia caused by diuretics: decreased serum sodium level > 10 mEq/L until < 125 mEq/L. - Hypo- or hyperkalemia caused by diuretics: changes of serum potassium level until < 3 mEq/L (hypokalemia) or > 6 mEq/L (hyperkalemia). - Unexplained muscle cramps.

part of diaphragm, which is usually covered with pleuroperitoneum. Hepatic hydrothorax is also considered as a marker of bad prognosis with approximately 8-12 months of mean duration of survival.[51,52] In hepatic hydrothorax, pleural effusion is usually found in the right pleura with transudate characteristic. Other common laboratory findings from pleural fluid analysis include < 250/mm^3 polymorphonuclear leukocytes (PMN) count, protein < 2.5 gram/dL, ratio between protein in the pleural fluid/serum protein < 0.5 with the gradient of serum albumin-pleural fluid > 1.1 gram/dL, and ratio between LDH in pleural fluid/serum LDH < 2:3. In the presence of spontaneous bacterial empyema, diagnosis can be established when positive result is obtained from pleural fluid culture accompanied with increased neutrophil count by > 250/mm^3 or negative result from pleural fluid culture accompanied with increased neutrophil count by > 500/mm^3.[5,50]

The first line management in hepatic hydrothorax is treating ascites by administering diuretics and/or LVP. Therapeutic thoracocentesis is indicated in refractory hepatic hydrothorax. To prevent the risk of re-expansion pulmonary edema, it is recommended to perform thoracocentesis without exceeding 2 liters of fluid in one session.[50] Nevertheless, due to the increased risk of pneumothorax, pleural and/or soft tissue infection, and bleeding, liver transplantation remains as the best therapeutic option for refractory hepatic hydrothorax. TIPS insertion has a role as a bridging therapy prior to liver transplantation. In conditions where liver transplantation or TIPS cannot be conducted, pleurodesis can be considered with success rate as high as 72%.[53] In cirrhotic patients with normal renal function and well-localized diaphragmatic defect, thoracoscopic procedure using mersilene mesh can also be considered.[54]

Hyponatremia

Hyponatremia is defined as serum sodium level < 130 mEq/L, which can be found in approximately 22% of cirrhotic patients. In liver cirrhosis, most hyponatremia events are caused by dilutional hypervolemia due to increased extracellular fluid volume. Vasodilatation of splanchnic artery in cirrhosis also contributes to decreased effective blood volume. Consequently, RAAS will be activated, leading to excessive release of antidiuretic hormone and, ultimately, reduced fluid excretion.[55] In patients without ascites and edema, usually hyponatremia hypovolemia is observed.[5] Hyponatremia has also been associated with worse prognosis, shown by its role in Model for End-Stage

Liver Disease-Natrium (MELD-Na) scoring. Utilization of MELD-Na scoring system is correlated with reduced mortality rate by up to 7% during waiting period for liver transplantation, in comparison to conventional MELD scoring system.[56]

Hyponatremia needs to be treated when serum sodium level reaches less than 130 mEq/L. Plasma volume expansion with saline solution is necessary in hyponatremia hypovolemia condition. On the contrary, the goal of therapy for hyponatremia hypervolemic is negative fluid balance, for instance through non-osmotic fluid restriction. Administration of hypertonic sodium chloride solution can improve hyponatremia in decompensated cirrhotic patients with special precautions in fluid overload condition. It is recommended to avoid administration of hypertonic sodium chloride solution exceeding 8 mEq/L in 24 hours to reduce the risk of osmotic demyelination syndrome. Liver transplantation remains as the definitive treatment for chronic liver disease with hyponatremia. Meanwhile, the use of intravenous albumin or selective antagonist of arginine-vasopressin V2 receptor in collecting duct still needs further studies.[5,57,58]

Spontaneous Bacterial Peritonitis (SBP)

SBP is defined as bacterial infection in ascitic fluid without any clear source of intraabdominal infection. Bacterial translocation from the gut, modified systemic defense mechanism, as well as deficiency of antimicrobial activity in ascitic fluid are the key factors in the pathogenesis of SBP. In liver cirrhosis, bacterial translocation often occurs due to bacterial overgrowth caused by disturbed transition inside the colon. Portal hypertension causes increased colon permeability through hypoxic mucous, oxidative stress, splanchnic vascular stasis, and congestion of the mucous layer of the colon. Disturbance in phagocytic activities of reticuloendothelial system represents the changes in systemic immunity. Moreover, low C3 level and low opsonization activity in ascitic fluid also contribute to low antimicrobial activity.[50] Diagnosis of SBP is established if increased absolute PMN count $\geq$ 250 cells/mm^3 is obtained from ascitic fluid analysis. This condition is known as neutrocytic ascites if there is no evidence of intraabdominal infection. If this result is accompanied with positive culture of ascitic fluid, then the condition is known as culture-positive neutrocytic ascites. In neutrocytic ascites with negative culture of ascitic fluid, the condition is called culture-negative neutrocytic ascites. If positive culture of ascitic fluid is obtained without neutrocytic ascites, then the condition is called bacterascites.[59] The most common etiologic bacteria are *Eschericia coli, Klebsiella pneumoniae*, and *Streptococcus pneumoniae*.[42]

Prognosis of patients with SBP is very atrocious with in-hospital mortality rate as high as 20%-40%. Therefore, early diagnosis and adequate treatment are highly compulsory for improving the prognosis. Empirical antibiotic therapy should be administered as soon as the diagnosis has been established, adjusted according to the possible etiologic microorganisms, severity of infection, and local antibiotic resistance profiles. In polymicrobial bacterascites, the third generation of cephalosporin can be given with additional anti-anaerobic therapy, such as metronidazole.[60] Administration of the third generation of cephalosporin demonstrated resolution of infection in 77%-98% of the patients.[61] As an alternative, amoxicillin/clavulanate also showed comparable resolution of infection and mortality rate with administration of cefotaxime, although higher number of drug-induced hepatitis was also observed.[62,63] Piperacillin/tazobactam or carbapenem also becomes drug of choice in nosocomial SBP or in regions where high level of resistance towards the third generation of cephalosporin is found.[42] Tigecycline or combination of tigecycline and carbapenem can be administered when *carbapenemase-producing* and *carbapenem-resistant non-carbapenemase-producing Enterobacteria* are suspected as the etiologic agent. In severe infection due to carbapenem-resistant and quinolone-resistant *Pseudomonas aeruginosa*, combination of amikacin and tobramycin or colistin-carbapenem/ceftazidime can be an option. If vancomycin-resistant *Enterococci* is suspected as the etiologic agent, administration of linezolid, daptomycin, and tigecycline can be conducted. It is also critical to perform

antibiotic de-escalation based on the results of microorganism culture to minimize the risk of antibiotic resistance.[64,65] It is recommended to evaluate the effect of antibiotic as early as 48 hours after the initial administration. Failure of the first-line antibiotic must be suspected when there is no improvement of clinical symptoms, or the absence of decreased white blood cells count by at least 25% in 48 hours.[5]

Aside from treatment, antibiotics also have a prominent role as prophylaxis of SBP. There are three populations who are deemed to have high risk of SBP, i.e., patients with acute gastrointestinal bleeding, patients with low protein level (< 1 gram/dL) in ascitic fluid without any history of prior SBP, and patients with history of prior SBP. Patients with history of prior SBP demonstrated cumulative recurrence rate in one year as high as 70%. Long-term oral administration of norfloxacin (400 mg/day) showed significant decrease of recurrence rate by 48%.[5] When norfloxacin is not available, 500 mg ciprofloxacin daily can be given as primary or secondary prophylaxis. Other alternative antibiotics are 960 mg trimethoprim-sulfamethoxazole daily per oral, 250 mg levofloxacin daily per oral, or intravenous 1 gram ceftriaxone daily.[66-68] Primary and secondary prophylaxis are recommended to be administered until ascites is resolved or liver transplantation can be performed or death.[68]

Renal Dysfunction

Acute Kidney Injury (AKI)

In liver cirrhotic patients, renal dysfunction is defined as a condition where serum creatinine level is at least 1.5 mg/dL or increased serum creatinine level by > 50% from the baseline with glomerular filtration rate (GFR) index ≤ 40 ml/min/1.73 m^2. Renal dysfunction can be found in the form of AKI or chronic kidney disease (CKD). In liver cirrhotic patients, AKI can be caused by diuretics, beta-blockers, vasodilator agents, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and other nephrotoxic drugs. In the condition of infection-induced AKI or AKI stage > 1A and the cause of AKI cannot be determined clearly, the intravenous administration of 20% albumin is recommended (1 gram/kgBW/day, maximum dose: 100 gram) for two consecutive days. For patients with AKI and grade 3 ascites, therapeutic paracentesis can be performed, and then followed by intravenous albumin administration. Other therapeutic options include renal replacement therapy (RRT) or kidney transplantation (**Figure 4**).[69,70]

Hepatorenal Syndrome (HRS)

HRS can be present with (HRS-AKI) or without AKI (HRS-NAKI).[69,71] HRS is mainly caused by renal hypoperfusion due to

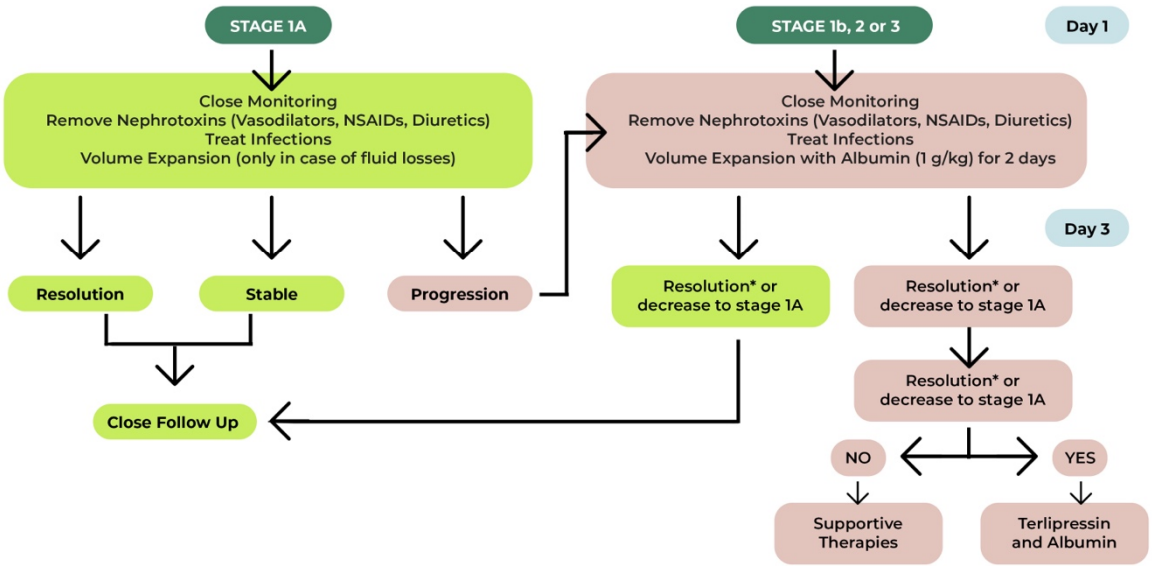

Figure 4. Management of renal dysfunction in cirrhosis (Adapted from [70]).

synergistic work between inflammation and microvascular disturbances in end-stage chronic liver disease. Both factors may amplify signals elicited by Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) on epithelial cells of proximal tubules. This process will lead to metabolic down-regulation mediated by mitochondria. Additionally, signal transduction will also change the priority of cell functions into prioritizing cell viability. RAAS activation and decrease of GFR also happen because of increased sodium chloride in macula densa. If the patient also has cholestasis, renal dysfunction will also be worsened since bile salts may trigger inflammation, disrupt circulation, and damage renal tubules.[72]

The first line of pharmacological management in HRS is vasoconstrictor and albumin (**Figure 4**).[70] An example of vasoconstrictor is terlipressin as a vasopressin analogue. Terlipressin also plays a role in decreasing stroke volume of patients with HRS. On the other hand, albumin has antioxidant and anti-inflammatory traits with recommended dose of 20-40 gram/day (adjusted according to the central venous pressure (CVP) measurement). Albumin administration is maintained until complete resolution (serum creatinine level < 1.5 mg/dL) for maximum duration of 14 days or partial resolution (decrease of serum creatinine level by ≥ 50%) or if no clinical changes are observed. It is also recommended to administer 1.5 gram/kgBW of albumin on the first day within 6 hours after diagnosis of SBP is confirmed and 1 gram/kgBW of albumin on the third day, in order to prevent AKI in patients with SBP.[5] Other choices of vasoconstrictors include noradrenaline, midodrine, and octreotide (**Table 8**).[73,74] TIPS placement can be considered in both HRS-AKI and HRS-NAKI, although its use is still limited and contraindicated in patients with severe liver failure.[75] RRT must be considered in patients with AKI, especially if there is acid-base imbalance or severe and/or refractory electrolyte imbalance. Continuous RRT has also demonstrated better contribution towards stability of heart and blood vessels compared to hemodialysis.[71] Nonetheless, the best definitive therapy for HRS is liver transplantation. Simultaneous Liver-Kidney Transplantation (SLK) is indicated in patients with liver cirrhosis and CKD with the following conditions:[5]

- Estimated GFR (with Modification of Diet in Renal Disease equation) ≤ 40 mL/min/1.73 m^2 or GFR measured by

Table 8. Recommended doses of vasoconstrictors in the management of HRS.[5,73,74]

	Terlipressin	Noradrenaline	Midodrine	Octreotide
Recommended dose	Initial dose for intravenous bolus: 0.5-1 mg every 4-6 hours. OR Continuous infusion dose 2 mg/day. After 2 days, the dose can be increased into maximum dose of 12 mg/day. OR Fixed dose (1 mg every 8-12 hours), increased by 2 mg every 4 hours.	Continuous infusion dose: 0.5 – 3 mg/hour. OR Initial dose: 0.5 mg/hour, increased by 0.5 mg/hour every 4 hours until maximum dose of 3 mg/hour (only if at least one of these targets are not achieved: increase of MAP by minimum 10 mmHg or increase urinary output > 200 mL/4 hours).	Initial dose: 7.5 mg/8 hours. Maximum dose: 15 gram/8 hours.	Subcutaneous dose: 50 ug/hour. Continuous infusion dose: 100-200 ug/8 hours.
Duration	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.

iothalamate clearance ≤ 30 ml/min/1.73 m^2.
- Proteinuria ≥ 2 gram/daily.
- Histopathological findings of the kidney: more than 30% glomerulosclerosis or more than 30% interstitial fibrosis.
- Hereditary metabolic disorders.

SLK is also indicated for patients with liver cirrhosis and AKI without any improvement (e.g., HRS-AKI which does not show any improvement after pharmacological management) with the following conditions:[5]
- AKI on RRT for ≥ 4 weeks, or
- Estimated GFR ≤ 35 mL/min/1.73 m^2 or measured GFR ≤ 25 mL/min/1.73 m^2 for at least 4 weeks.

Acute Variceal Bleeding

Acute variceal hemorrhage (AVH) is defined as variceal bleeding in patients with confirmed or suspected portal hypertension, with the presence of hematemesis and/or ongoing melena within 24 hours upon admission. Generally, the timeframe of AVH episode is 48 hours. The main principle of AVH treatment is preventing recurrent bleeding episode and death (**Figure 5**).[35] Fluid replacement therapy must be initiated as soon as possible to return hemodynamic stability. The recommended fluids are crystalloid or colloid. To date, starch is not recommended as an option for fluid replacement therapy. Administration of restrictive blood transfusion can be done if the patient had low hemoglobin level (< 7 gram/dL) with target of hemoglobin level post-transfusion: 7-9 gram/dL.[5,73]

Currently, non-selective beta-blocker (NSBB) has a role as primary prophylaxis, while Endoscopic Band Ligation (EBL) plays a role as secondary prophylaxis (**Table 9**)[76] to prevent variceal bleeding in high-risk cirrhotic patients. Propranolol and nadolol manage portal hypertension by decreasing stroke volume and splanchnic blood flow. Simultaneously, the effect of alpha-1 adrenergic receptor also triggers splanchnic vasoconstriction, and thus,

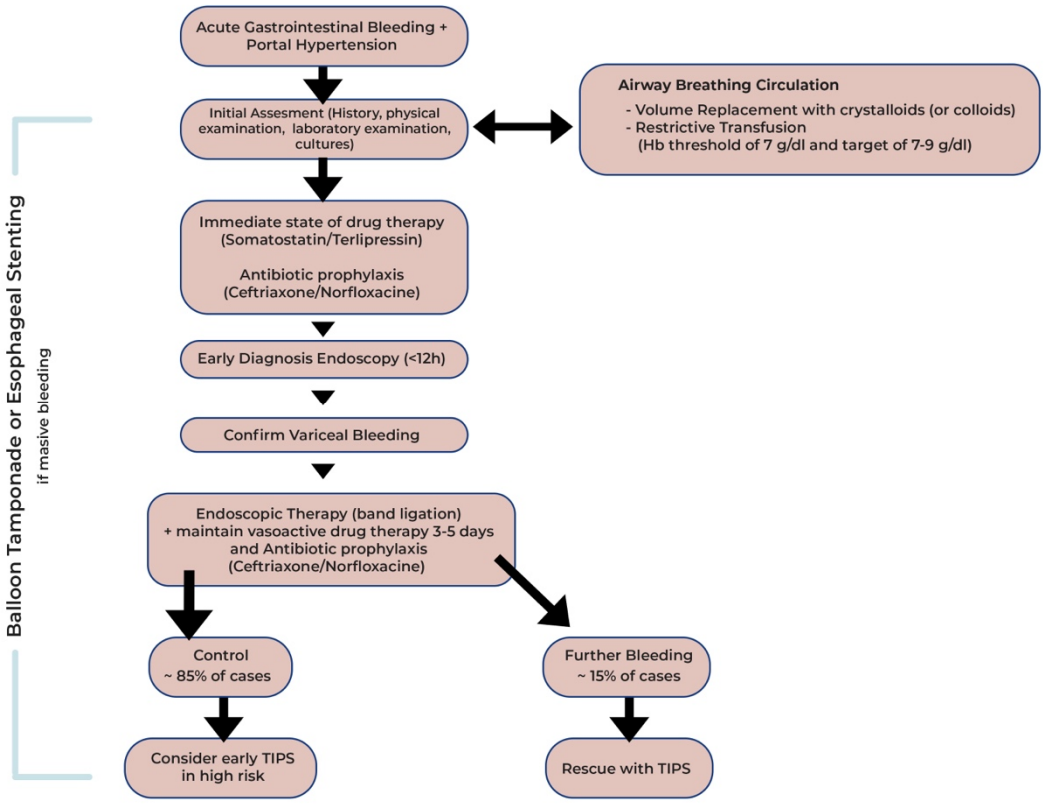

Figure 5. Treatment algorithm of acute gastrointestinal bleeding in liver cirrhosis (Adapted from [5]).

Table 9. Prophylaxis for preventing recurrent variceal bleeding.[5-6,76]

Therapy	Recommended Doses	Therapeutic Goals	Maintenance Therapy
Propranolol	20-40 mg (twice daily) → adjust the dose in 2-3 days. Maximum daily dose: 320 mg/day in patients without ascites or 160 mg/day in patients with ascites.	Resting heart rate: 55-60 beats/minute. Systolic blood pressure should not be lower than 90 mmHg.	Continue therapy for maintenance.
Nadolol	20-40 mg once daily. Dose adjustment: 160 mg/day in patients without ascites or 80 mg/day in patients with ascites.	Resting heart rate: 55-60 beats/minute. Systolic blood pressure should not be lower than 90 mmHg.	Continue therapy for maintenance.
Carvedilol	Initial dose: 6.25 mg once daily. After 3 days, the dose can be increased to 6.25 mg (twice daily). Maximum dose: 12.5 mg/day (in patients with persistent arterial hypertension, the dose can be increased until 12.5 mg twice daily or 25 mg/day).	Systolic blood pressure should not be lower than 90 mmHg. Decreased heart rate should not be a reference for dose titration.	Continue therapy for maintenance.
EBL	Every 2-8 weeks until varices can be eradicated.	Until varices can be eradicated	The first EGD should be performed within 3-6 months after varices has been eradicated and every 6-12 months afterwards.

decreasing portal pressure. Carvedilol can also be an alternative to lower intrahepatic resistance and porto-collateral blood flow.[5,6] NSBB must be halted when severe hyponatremia occurs (serum sodium level < 130 mEq/L), or if the mean of MAP is low (< 65 mmHg), or if the stroke volume is low with systolic blood pressure < 90 mmHg, or if serum creatinine level is increased by > 1.5 mg/dL. Carvedilol or high-dose NSBB is also recommended to be avoided in severe or refractory ascites. In the condition of intolerance towards NSBB, EBL can be performed. Combination of NSBB and EBL can also be an option for secondary prophylaxis with higher therapeutic efficacy in comparison to monotherapy. The therapeutic efficacy of this combination is also comparable with TIPS in preventing bleeding episode.[5,73]

Aside from fluid replacement, vasoactive agents and antibiotics also need to be administered as early as possible to control active bleeding and increase the possibility of survival. Recommended vasoactive agents include terlipressin, somatostatin, and octreotide (**Table 10**).[5] Bolus of intravenous somatostatin or octreotide can still be administered if bleeding episode still occurs. When AVH diagnosis has been confirmed, vasoactive agents can be continued for 5 days to prevent early recurrent bleeding (**Table 11**).[77] Shorter duration of vasoactive administration (48-72 hours) is contemplated when the bleeding episode is not too severe. Endoscopic examination is recommended to be conducted as soon as blood volume resuscitation and hemodynamic stability have been achieved (within 12 hours after hospital admission).[78] Combination between endoscopic therapy and vasoactive agent has more efficacy compared to monotherapy due to local hemostatic effect from endoscopic therapy and portal pressure lowering effect from vasoactive agents.[79] Cyanoacrylate injection is currently recommended as an endoscopic therapy for patients with gastric varices (cardio-fundal varices).[80] In addition, fluoroscopy-guided coil insertion and/or cyanoacrylate injection can also be done to treat fundal varices (**Table 12**).[5,77,81]

It is also important to remember that variceal bleeding can lead to several morbid complications, such as bacterial infections, hepatic encephalopathy, and renal dysfunction. Antibiotic prophylaxis is recommended to lower the incidence of secondary infection, control

Table 10. Recommended doses of vasoactive agents for acute variceal hemorrhage management.[5]

Therapy	Recommended Doses	Duration of Therapy
Octreotide	Initial IV bolus 50 ug (can be repeated within the first one hour if bleeding persists). Continuous infusion: 50 ug/hour.	2-5 days.
Somatostatin	Initial IV bolus 250 ug (can be repeated within the first one hour if bleeding persists). Continuous infusion: 250-500 ug/hour.	2-5 days.
Terlipressin	Within the first 48 hours: 2 mg intravenous until bleeding can be controlled. Maintenance dose: 1 mg intravenous every 4 hours to prevent recurrent bleeding.	2-5 days.

Table 11. Clinical definitions of acute and recurrent variceal bleeding.[77]

Clinical Conditions	Timeframe from T_0	Subtypes	Timeframe from T_0
Acute variceal bleeding	48 hours	Active (based on endoscopic examination)	48 hours
Recurrent bleeding	After 48 hours	Inactive (based on endoscopic examination)	48 hours
		Very early recurrent bleeding	48-120 hours
		Early recurrent bleeding	6-42 days
		Late recurrent bleeding	After 42 days

Table 12. Classification, prevalence, and bleeding risk of gastric varices.[77]

Types	Definition	Relative Frequency	Risk of Bleeding Without Therapy
GOV1	Esophageal varices extended until lower cardia towards minor curvature.	70%	28%
GOV2	Gastroesophageal varices extended until lower cardia towards fundus.	21%	55%
IGV1	Isolated varices on fundus.	7%	78%
IGV2	Isolated varices in locations other than gaster.	2%	9%

the bleeding, and increase life expectancy.[6] The first line antibiotic for patients with advanced cirrhosis, who are consuming quinolone as a prophylaxis with history of hospitalization in a healthcare center with high prevalence of quinolone resistance, is intravenous ceftriaxone (1 gram/day) for 7 days. Oral quinolone can be given if the patient cannot tolerate ceftriaxone (**Table 13**).[66] In 10-15% cases, where AVH still persists or becomes recurrent despite the administration of vasoactive agents and antibiotic prophylaxis combined with EBS, TIPS should be considered as a salvage therapy.[6] If TIPS cannot be performed, endoscopic therapy can be conducted for the second time with optimalization of vasoactive drugs and 2-fold increase of somatostatin dose and/or replacement with terlipressin. Balloon tamponade or self-expanding esophageal stents can also be placed as an alternative bridging therapy.[82]

Table 13. Recommended doses of antibiotic prophylaxis in acute variceal bleeding.[5,66,78]

Therapy	Recommended Doses	Duration of Therapy
Ciprofloxacin	500 mg per oral twice daily OR 400 mg intravenous twice daily,	3-7 days
Ceftriaxone	1 gram daily.	7 days

Others

Coagulopathy

Vitamin K deficiency is commonly found in decompensated cirrhotic patients, which is affected by a complex mechanism involving bile salt deficiency, failure in bile salt secretion, and the use of broad-spectrum antibiotics. Nowadays, vitamin K injection 10 mg daily for 3 days is recommended as an adequate option to treat vitamin K deficiency in decompensated cirrhotic patients. Prophylactic correction of prothrombin time with Fresh Frozen Plasma (FFP) remains controversial due to a significant number of adverse events, e.g., fluid overload, exacerbation of portal hypertension, increased risk of infection, or acute liver injury related to transfusion. Platelet transfusion can be considered when platelet count is lower than 50,000/mm^3 with platelet count target > 70,000/mm^3. Maintaining low CVP and reducing portal pressure can also be helpful during surgical management. Other options for bleeding control are topical hemostatic agents, aprotinin, tranexamic acid, and epsilon caproic amino acid, which may have a role in controlling local bleeding. These agents, however, still need further trials due to higher thrombotic risk.[83]

Portal Hypertension Gastropathy (PHG)

PHG is commonly found in decompensated cirrhotic patients. The presence of esophageal varices and Child-Pugh B or C category can also predict the incidence of PHG.[84] Diagnosis of PHG can be confirmed by endoscopic examination, from which mild subtype of PHG usually appears with mosaic pattern or may overlap with red signs (severe subtype of PHG). PHG is usually located on the proximal part of gaster (fundus and corpus).[85,86] In the progression of chronic liver disease, PHG plays a critical role since it may cause occult bleeding, which ultimately leads to chronic iron deficiency anemia. PHG can also be an incidental asymptomatic finding in the absence of gastric or esophageal varices.[35] The first line therapy for chronic bleeding with PHG is NSBB. Iron supplementation and/or blood transfusion can also be given according to the clinical indications.[5] In patients with refractory PHG and compensated cirrhosis, TIPS placement can improve endoscopic findings, as well as lower the requirements for blood transfusion. Additionally, similar to AVH, antibiotic prophylaxis can also be administered to patients with acute PHG bleeding.[87] An electrosurgical technique, called Argon Plasma Coagulation (APC), has emerged as an option to manage bleeding episodes and devitalization of abnormal tissues. Previous evidence indicated higher hemoglobin level and lower blood transfusion requirement after APC.[88,89] Although further validations are still required, rebamipide has been proposed as a potential therapeutic agent for PHG due to its antioxidant effect (free radicals scavenging), ability to decrease nitration process of tyrosine residues from Extracellular Signal-Regulated Kinases (ERK), and mucosal healing capability.[90]

ACKNOWLEDGMENTS

We want to express our gratitude towards all chairmen from twenty branches of Indonesian Association for the Study of the Liver, who had contributed their time, contribution, and advices in developing this national consensus.

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