EAS Journal of Anaesthesiology and Critical Care
Abbreviated Key Title: EAS J Anesthesiol Crit Care
ISSN: 2663-094X (Print) & ISSN: 2663-676X (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-8 | Issue-1 | Jan-Feb-2026 | DOI: https://doi.org/10.36349/easjacc.2026.v08i01.007

Review Article

Management of Variceal Bleeding in Cirrhotic Portal Hypertension

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Article History
Received: 02.12.2025
Accepted: 27.01.2026
Published: 03.02.2026

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: Management of the variceal bleeding is common and often life threatening complication of cirrhotic portal hypertension. The more than three decades have markedly improving in the management of the cirrhotic portal hypertensive variceal bleeding due to the better overall care in the acute setting, updated treatment guidelines, specially use covered stent in TIPS, involves multidisciplinary expertise, and better understanding mechanism of portal hypertension. The best mortalities for prophylaxis and treatment of variceal bleeding due to the cirrhotic portal hypertension were reviewed in numerous of clinical studies and follow treatment guidelines.

Keywords: Cirrhotic Portal Hypertension, Variceal Bleeding, Secondary Prophylaxis, Gastroesophageal Varices, Evidence-Based Guidelines.

1. INTRODUCTION

Cirrhotic portal hypertensive variceal bleeding is the most common complication of chronic liver disease. The most common causes of cirrhosis are viral hepatitis (HBV & HCV) and alcohol abuse. The complications of liver cirrhosis result in a large number of deaths worldwide every year. According to the Global Burden of Disease study in 2017, more than 1.32 million cirrhosis-related deaths were reported, accounting for around 2.4% of all deaths worldwide [1]. Portal hypertension with liver cirrhosis being the most common (>90%) cause worldwide [2], can also occur in the absence of liver cirrhosis known as non-cirrhotic portal hypertension [3]. Cirrhosis is divided into two stages: compensated and decompensated liver cirrhosis, ranking among the top eight causes of death in the United States in 2010 [4]. The median survival rate for compensated liver cirrhosis patients is more than 12 years, while patients with decompensated liver cirrhosis have a median survival rate of less than 2 years [5]. The majority of complications of cirrhotic portal hypertension occur in patients with decompensated liver cirrhosis, including esophageal and gastric variceal bleeding, ascites, hepato-renal syndrome, bacterial peritonitis, hepato-pulmonary syndrome, and hypersplenism [6-9].

The hepatic venous pressure gradient (HVPG) is a significant indicator of portal hypertension, and its reduction indicates an improvement in portal hypertension and the risk of variceal bleeding [9]. The normal hepatic venous pressure gradient is usually 1 to 5 mmHg, with portal hypertension defined as a hepatic venous pressure gradient above 5 mmHg. Clinically significant complications of portal hypertension occur at levels above 10-12 mmHg, such as variceal bleeding and ascites [10]. Acute variceal bleeding often occurs when HVPG is above 20 mmHg, predicting failure to control bleeding and a higher rate of mortality [11-14]. Commonly used methods to reduce HVPG include non-selective beta-blockers (NSBBs), vasopressors, and transjugular intrahepatic portosystemic shunt (TIPS).

Esophageal and gastric variceal bleeding are the most common clinical complications of cirrhotic portal hypertension, with a mortality rate of 25% to 50% in patients with portal hypertension [15-17]. Gastroesophageal variceal bleeding accounts for approximately 80% of all cases of portal hypertension with liver cirrhosis, and 20% of patients with portal hypertension and acute variceal bleeding die within 6 weeks. The rate of re-bleeding ranges from 30% to 40% at 6 weeks, and the mortality rate is 30% among re-bleeding patients [18, 19].

Over the past three decades, there has been a significant improvement in survival rates and advances in the management of cirrhotic portal hypertension variceal bleeding and acute variceal bleeding. The improved survival rate of variceal bleeding patients with cirrhotic portal hypertension over the past 30 years is due to improvements in several factors, including earlier general supportive management, early use of NSBB and

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vasopressors, endoscopic therapy, quality of critical and high dependency care, endovascular intervention therapy, and intensive care medicine.

In this overview, we focus on the currently used therapeutic approaches in the management of variceal bleeding due to cirrhotic portal hypertension. We have reviewed retrospective studies, prospective studies, meta-analyses, and randomized controlled trials. The management of esophageal and gastric variceal bleeding due to cirrhotic portal hypertension, primary and secondary prophylaxis, and UK guidelines for managing variceal bleeding in cirrhotic patients [20], portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis and management: 2016 practice guidance by the American Association for the Study of Liver Disease [20]. We retrieved all articles from PubMed, Google, and Google Scholar. Search items included management of gastroesophageal bleeding, portal hypertension, esophageal and gastric varices, and management of variceal hemorrhage.

2. Incidence and Prevalence of Cirrhotic Portal Hypertensive Variceal Bleeding

Variceal bleeding occurs in approximately 50% of cirrhotic patients. The prognosis of cirrhotic portal hypertensive variceal bleeding depends on the severity of liver disease. The incidence of variceal bleeding over 10 years is 44% using a competing risk model [21]. In cirrhotic patients without varices, the rate of development is approximately 8% per year with the main risk factor for varices being a hepatic venous pressure gradient of more than 10 mmHg [10]. The rate of small varices developing into large varices is 8% per year, with decompensated liver cirrhosis being a major risk factor for large varices [22]. When the hepatic venous pressure gradient is less than 12 mmHg, there is a lower chance of variceal bleeding. However, with a hepatic venous pressure gradient of more than 12 mmHg, patients have a higher chance of variceal rupture [11-23]. Patients with a hepatic venous pressure gradient of more than 20 mmHg may experience variceal bleeding within 24 hours, a high chance of recurrent bleeding within one week, and a high risk of failure to control variceal bleeding as well as a 12 month mortality rate [24, 25].

The management of gastric variceal bleeding is a clinical challenge and less prevalent than esophageal variceal bleeding. Gastric varices are less likely to rupture and bleed than esophageal varices, but when they do, they require blood transfusion and have a higher mortality rate than esophageal variceal bleeding [15-26]. The overall incidence of cirrhotic gastric varices in patients who have never previously bled is 4%. A previous study reported that on endoscopy screening for cirrhosis, 25% of patients had gastric varices and 18% had both gastric and esophageal varices [27]. The incidence of bleeding from gastric varices is about 25% per year, with higher bleeding associated with the fundus of the stomach. Some relatively risk factors for gastric varices include large size of varices, Child-Pugh B and C, HVPG > 12 mmHg, and endoscopic appearance of red spots [15-27].

3. Causes of Cirrhotic Portal Hypertensive Variceal Bleeding

1. Chronic hepatitis B and C
2. Alcoholic liver disease
3. Non-alcoholic steatohepatitis
4. Primary biliary cholangitis
5. Primary sclerosing cholangitis
6. Autoimmune hepatitis
7. Fatty liver disease
8. Veno-occlusive disease
9. Schitosomisis
10. Hereditary hemochromatosis
11. Hepatictocxic drugs
12. Cystic fibrosis
13. Alpha 1-antitrypsin deficiency
14. Nodular regenerative hyperplasia
15. Others

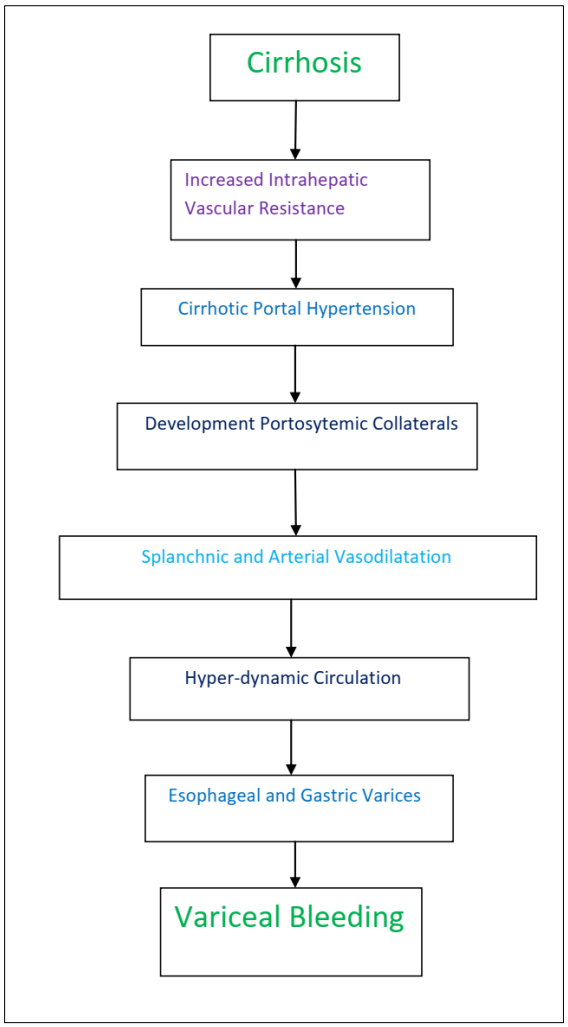

Figure 1: Pathophysiology of Cirrhotic Portal Hypertension with Esophageal and Gastric Vasrices

4. Pathophysiology of Cirrhotic Portal Hypertension:

The venous blood flow from the large intestine, small intestine, stomach, spleen, and pancreas drains via the portal vein into the liver. The portal vein blood reaches in the hepatic sinusoids, which then drain into the hepatic veins to IVC. In liver cirrhosis, the liver tissues are damaged and regenerate in nodules of hepatocytes, disrupting the normal function of the hepatic sinusoids. This impairment lead to a decrease in venous blood drainage through the hepatic sinusoids, resulting in an increase in the pressure gradient between the portal vein and hepatic vein.

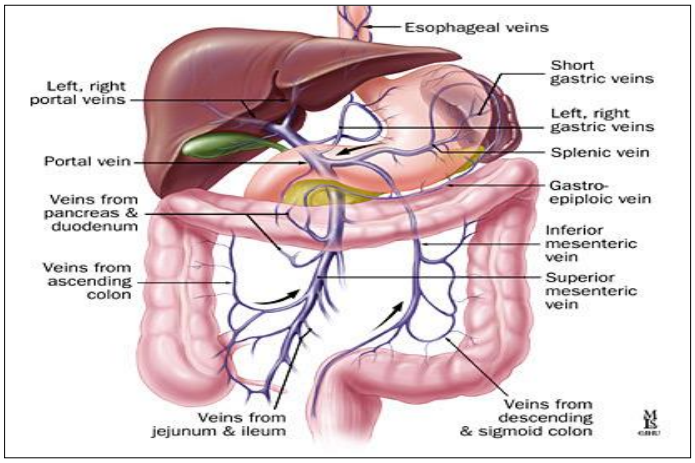

Figure 2: Portal venous systems (The portal vein blood supply extends from guts capillaries, spleen vein, and gastric vein to the hepatic sinusoids)

In cirrhosis, cirrhotic portal hypertension is due to the combination of intrahepatic vascular resistance and increasing blood flow in the portal venous system. The intrahepatic vascular resistance increases in two ways: mechanically intrahepartic vascular resistance and dynamically through intrahepatic vascular resistance. The mechanical intrahepatic vascular resistance is due to the development of intrahepatic fibrosis; various pathologic processes contribute to increased intrahepatic venous resistance at the level of the hepatic microcirculation, such as regenerative nodules and architectural distortion in hepatic sinusoids [28]. Dynamic intrahepatic vascular resistance results from vasoconstriction in the portal venous system secondary to activated hepatic stellate cells and smooth muscle cells [29].

Intravascular resistance is modulated by endogenous vasoconstrictors (e.g. norepinephrine, angiotensin-II, endothelin-I, and thromboxane $A_{2)}$ and vasodilators (e.g. nitric oxide). This results in an imbalance between vasoconstrictors and vasodilators. In portal hypertension there is an increase in cardiac output and a decrease in systemic vascular resistance (30), leading to a hyper-dynamic circulation state with splanchnic and systemic arterial vasodilatation. Splanchnic venous vasodilation results in increased blood flow in the portal system. Splachnic venous vasodilator. Excessive release of nitric-oxide from splenic venous vasodialator lead to severe portal hypertension.

4.1 Increased Intrahepatic Vascular Resistance:

It is a result of both fixed obstruction created by hepatic structural changes and alterations in hepatic vascular tone. The vascular structure is obliterated by scar tissue formation and regenerate nodules during the demodulated tissues in cirrhosis; accounting for approximately 70% of the increased hepatic resistance [31, 32]. Activated hepatic stellate cells respond to excessive extracellular matrix it formation, contributing to scar tissue formation in liver cirrhosis. This scar tissue is eventually replaced by functional liver tissue with a fibrous matrix [33-35]. The remaining 30% of hepatic resistances is attributed to the contraction of hepatic stellate cells and vascular muscle cells, which are modulated by vasoconstrictors [36, 37]. Hepatic vascular tone is further affected by endothelial dysfunction, characterized by reduced intrahepatic bioavailability of vasodilators such as nitric oxide and increased release of vasoconstrictors [31-38].

4.2 Portal Tree:

It constitutes a tree of conducting small blood vessels terminate into the venules, and it inner diameter is 400 μm. The conductive portion of the portal tree is preterminal portal venules. The distal portion vessels have inner diameter of 80-40 μm appear to be main site of the constrictive response in portal tree to various stimulators, and it main mechanism is control blood distribution in the liver. Thereafter downstream, a portion called terminal portal venules and it does not contract but, it can splits into septal, then perilobular and lobular branches are supply venous blood to sinusoids through the inlet venules. It can be identified a special sphincteroid mechanism altering the regional supply in the sinusoids net and the sphincters are created by the nuclei of the endothelial cells is residing at entrance in sinusoids, where is protrusion can be changed to variably impeded flow of blood.

4.3 Sinusoids:

The most common cause of sinusoids is parenchymal liver disease and more than 90% cause by cirrhosis of liver disease. It is characterized by the presented with parenchymal fibrosis and regenerating nodules. The interdigitating networking of afferent and efferent blood vessels, there have spaces fill with plates and columns of hepatocyte, which is a complex network of sinusoids. The sinusoids exchange portions of liver circulation is spaces than the other capillary beds. Its endothelial lining made with flat, lobulated, and fenestrated cells. These are overlapping loosely without attachment each other. The fenestrations is more than 2 μm in diameter, where is occupying about 10% of wall surface and it not allow to obstacle to plasmatic macromolecules. There have enable exchange of water and substances in sinusoids due to quite low hydrostatic pressure. The caliber of sinusoids is variable, size is 7 to 15 mm, and however, it can be increase 180 mm. The changed of caliber usually depends on regional blood flow and volume. In the physiologically there have only scant extracellular matrix but, there have no connective tissues in the space. So, no more space for its enlargement. It is approximately 80% of the sinusoids have obliterate by portal pressure [39].

4.4 Sinusoidal Resistance:

The chronic liver disease can be lead to hepatic fibrosis and liver cirrhosis is commonly presented. It is clinically important etiopathogenetic base of cirrhotic portal hypertension. The morphologically and functionally changed in liver circulation and consequence the increase in portohepatic vessel resistance. The basis of vessels resistance flow reflects in both stage of the liver disease [40]. It's affected in both mechanism component and dynamic component. The mechanism component gains significantly when in an advanced stage of liver disease.

4.4.1. Mechanism Component:

The increased hepatic vascular resistance in cirrhotic liver disease, and different role of varying phases of the pathophysiolological process. Which destruction of the liver tissues and reduce in cross-sectional area of the hepatic microcirculation. Other hand, cellular volume of individual hepatocyte significantly increased with cellular edema in particular type such as in acute alcoholic, thereafter, significantly narrowing the sinusoidal lumens [40, 41]. The crucial

structural is change in the sinusoidal lining and structural of lobules. After then collagen formation in the space of disse, and accompanied by hug changes in endothelium. It leads to increase in blood flow resistance without change of vascular lumen [41-43]. The quantitatively reduce of sinusoidal in the lobules and narrowing with hepatocytes, which is regenerate multi-layer trabeculae. After then development regenerated nodules compressed both functionally sinusoid and intraparenchymal portohepatic shunts, as well as central venules, smaller portal veins and hepatic veins [39].

4.4.2. Functional Component:

In this functional component, no significant flow resistant can expected in portal tree, and find out the site of increased portohepatic resistance in sinusoids. The react to varying vasoactive agents such as, nitric oxide, endothelins, thromboxane A2, substance P, angiotensin II, nor-epinephrine and thrombin. The cells are development the features of the myofibroblast in scarring tissue after stimulation, and changed the properties of the sinusoids due to formation hug of amount of extracellular matrix. It can exert constriction strongly to altering in sinusoidal blood flow in the inflammation part. There associated receptors are indicates that cellular transformation can be initiated by local inflammatory mediators and cytokines that can modulated due to other paracrine substances [44, 45]. The substantially increasing is seen in their sensitivity to vasoactive substances.

4.5 Presinusoidal Resistance:

It is usually causes by portal or spleen vein thrombosis and represented with secondary sign of portal hypertension (e.g. splenomegaly, portosystemic collateral, and ascites). The hepatocyte and acinar are not affect by the pathogenetic process. But, liver functions are also not normal due to portion of the portal blood bypass the hepatic biological filter. The pathological process can affected the portal spaces and overlap into sinusoids. It can develop as results of infiltration in portal spaces by hematopoetic tissue or thrombosis in terminal branch of portal vein [46]. Some substances can be toxicity injuring pericytes and endothelium at the junction of the portal venous and sinusoid. It can increase portal vascular resistance, and these substances are arenic, vinylchloride, cytostatics, copper, and vitamin A. The portal sclerosis and fibrosis can be cause endothelial damage in venules and sinusoids, such as Banti syndrome. Enlargement of spleen with mild portal hypertension can be attribute to infiltration of perisinusoidal lymphocyte and hyperplasia of kupffer cell [47].

4.6 Postsinusoidal Resistance:

It is usually causes by veno-occlusive disease, Budd-Chiari syndrome and cardiac insufficiency. It presented with diffuse or dispersed obstructions of hepatic venous tree and veno-occlusion diseases. These are non-cirrhotic and non-nodular processes pathophysiology that are etiologically heterogeneous. The clinical outcomes are depending on development of venous obstruction in vein and nature of underling disease. The sequence of the liver damage is owing to reducing in hepatic perfusion in liver.

4.7 Splanchnic Vasodalation:

It is leading to increase portal blood flow and also contributing the pathogenesis of portal hypertension. The presence of endothelium dysfunction to vasodilators in hepatic vascular in cirrhotic splanchnic vessels, and vasodilators is promote to local over production of vasodilators, which are intrinsic vascular hypocontractillity allow to increase blood flow through the splanchnic vessels. When decreasing portosystemic resistance thereafter the development of portosystemic collaterals and increase flow through the splanchnic vessels to be needed for maintain portal pressure as clinically adequate level. This pathogenesis is still speculative. There have some hyperactivity of local vasodilatation agents; prostacyclin ($PGI_{2)}$ and PGE_2 [48]. There have also significant role of adenosine and histamine and it play important role to credited gastrointestinal hormones and mediators such as glucagon, vasoactive intestinal peptide.

4.8 Development of Portosystemic Collaterals:

The developments of the vascular network portosystemic collaterals can be accompanying the portal hypertension in cirrhosis. Development of collaterals owing to activated of angiogenesis that is modulated by several growth factors such as platelets derived growth factor, pigmented epithelial derived factor, Vascular endothelial growth factor (VEGF), placental growth factor [31-51]. It is an automatically pathophysiological consequence of the increased portosystematic gradient after severe portal hypertension. The increasing pressure gradient, flow through preformed vessels, with minimum caliber and naturally increase. The reaction of endothelial by bloodstream is leading to formation of paracrine agents, such as nitric oxide (NO), prostacyclin. Which is apart from causes the dilation or remodeling of local vascultures. The regulating nitric oxide in the splachnic vasculatures can play a role in formation of portosysytemic collaterals [52].

The nicotinamide adenine dinucleotide phosphate oxidase can also play an important role in cirrhotic portal hypertension by modulated splanchnic venous angiogenesis and collaterals formation [53]. The quality of development and distribution of collaterals are closely associated with complications of cirrhotic portal hypertension. The drains blood from the splanchnic venous bed to direct in systematic circulation and by passing the functional liver parenchyma. Site of portosystemic collaterals: The collaterals are develop when portal pressure gradient is increased and it can be classified into three groups; (1) gastro-esophageal and hemorrhoid plexus; (2) paraumbilical venous in around falciform ligaments; (3) poryorenal plexus.

4.9 Esophageal and Gastric Varices:

The portosystemic collaterals are can formation in several parts, among them gastroesophageal junction is most threatening aspect of portal hypertension. Twenty percentages of patients have medium or larger varices in gastroesophageal junction at the time of diagnosis of liver cirrhosis, and overall 80% patients development during the several time follow up [54]. The prognosis of variceal bleeding depends on severity of liver cirrhosis and treatment of cirrhotic portal hypertension. The one third of cirrhotic portal hypertensive patients with documented the episode of variceal bleeding usually within 2 years after the diagnosis, and a quarter of half of portal hypertension patients cannot survive life [55]. The risk of re-bleeding is higher within 6 weeks after first episode of variceal bleeding with more than 25 % - 30 % mortality.

The site of gastro-esophageal junction has relatively closely relation of portal and systematic venous system. The critical site of bleeding is several centimeters above and below the esophageal sphincter. The veins are in this area penetrated with mucosal layer, and not sufficient support of the vessels wall to protect from uncontrolled dilatation and rupture varices. Once variceal bleeding is occurring then there intravariceal blood pressure is causes progressive enlargement of the diameter of varices. The vascular wall becomes thinner and irregular. On endoscopic examination red sign is warning of variceal bleeding. The intramural variceal wall is determining the risk of rupture of the varices. The intramural tension of the variceal wall is not possible to measuring direct forcefully, it need to follow the law of laplace described; (1) intravariceal pressure, (2) variceal diameter, (3) thickness of the variceal wall. These parameters can be reliably measure by high specialization center due to high risk of chance of the variceal bleeding so, it need to emergency well management of the variceal bleeding.

4.10 Pathophysiology Bases on Treatments of Cirrhotic Portal Hypertension:

portal venous pressure initially as consequences of increase intrahepatic venous resistance to portal blood flow attributed to mechanisms component (e.g. vascular distortion by regenerative nodules and microthrombi), which involved 70% of the intrahepatic resistance, it can treat accordance etiology of the liver cirrhosis with use antifibrotic agents and anticoagulant drugs [31]. One-third of the intrahepatic venous resistances are attributed to an increased intrahepatic vascular tone, resulting reduced nitric oxide bioavailability [56]. This dynamic component is controllable to vasodilators (e.g. angiotensin-II, alpha-adrenergic antagonists). A conceptually more applicable to dynamic component is to use drugs such as statins. Statins have advantages of vasodilatation, improve in blood flow and liver function and also have antifibrotic properties [31].

The initially sequel of the portal hypertension is formation of portosystemic collaterals, which is most commonly develop through coronary or gastric veins and represent gastricesophageal variceal. Although formation of collaterals had been assume to be the consequence of dilatation of preexisting vascular channels. Development of collaterals and splanchnic vasodilatation lead to increase flow into intestine and portal venous system. The nitric oxide formation is the major causes of vasodilatation and increased splanchnic blood flow. Vasodilatation also effect in the systematic circulation and it can lead to activation of neurohumoral and vasoconstrictive system, sodium and water retention, increase blood volume, and increase cardiac output. Furthermore hyperdynamic circulation state that increased portal venous flow and portal pressure.

Drugs are used for splanchnic vasoconstriction: non-selective beta-blockers (propanolol, nadolol, and carvedilol), vasopressin (analogue terlipressin), and somatostatin (analogues octreoytide and vapreotide) are known to treatment of portal hypertension and variceal bleeding Figure 2.

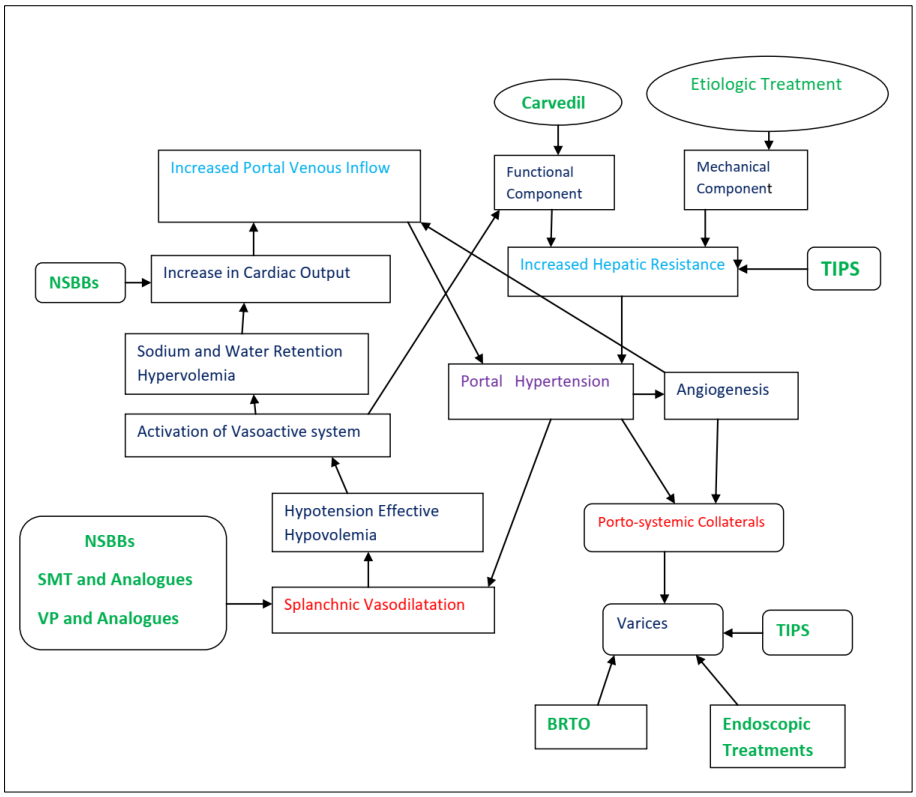

Figure 3: Pathophysiology bases on Treatment of Cirrhotic Portal Hypertension

Endoscopic variceal ligation is a procedure that uses elastic bands to treat the esophageal variceal bleeding in repeated sessions until stop bleeding. Sessions are repeated at 7 and 14 days in intervals until variceal obliteration (usually requires 2 or 4 sessions). It is a local therapy that has no effect of portal pressure. It has been shown to significantly lower re-bleeding and lower frequency of esophageal strictures. However, patients are requires to indefinite endoscopic monitoring.

The local therapies for gastric variceal bleeding are (1) injected cyanoacrylate glue, (2) transvenous obliteration by liquid embolic agents or sclerosants agents into gastric/splenorenal collateral through the left renal vein aided by balloon occluded retrograde transvenous obliteration (BRTO), (3) Transjugular intrahepatic portosystemic shunt (TPIS).

In the patients with decompensated cirrhosis, portal pressure more than 20 mmHg with high chance of re-bleeding, and failure of endovascular variceal ligation and pharmacological therapy after then placement of the transjugular intrahepatic portosysytemic shunt (TIPS). TIPS can significantly reduce portal pressure and variceal bleeding. Therefore, patients with functional stent used, there is not requires others treatments for portal hypertension (e.g. NSBB and EVL).

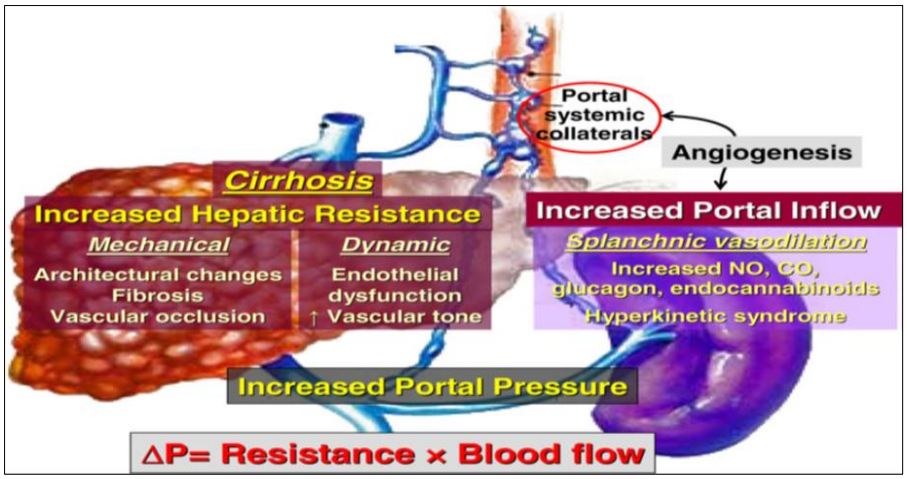

Figure 4: Pathophysiology of Portal Hypertension
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5. Diagnosis and Clinical Manifestation of Cirrhotic Portal Hypertensive

The patients with cirrhotic portal hypertension usually repotted chronic liver disease causes by hepatitis B or C or alcoholic abuse. On the physical examination unless presents with esophageal varices or with ascites, the portal hypertension can suspected from indirect signs; multiple spider nevi on the skins, dilate veins on anterior abdomen and prominent of palmar erythema. On the examination can diagnosed with enlarge or small hard liver on palpation and an enlargement of spleen. The clinical manifestations of decompensated cirrhosis liver including; varices and variceal bleeding, ascites hepato-renal syndrome have directed related to the development of the hyper-dynamic circulation and splanchnic vasodilatation. The develop of decompensation events is related with a reduction in the medial survival rate of the patient to less than 2 years and more than 12 years median survival rate in without complication of the cirrhotic portal hypertension [57].

Laboratory Finding; serum bilirubin high, gamma glutamyl transpeptidase high, twofold above normal increase in alkaline phosphatase, slightly elevated transaminases, hypoalbuminemia, thrombocytopenia, prolonged prothrombin time, hyper gammaglobulinemia, leucopenia and macrocytic anemia are usually present.

On ultrasound examination; an enlargement of spleen due to portal hypertension, dilated portal vein and its tributaries, change in size in liver with an abnormal echoic of parenchyma of liver. Color Doppler ultrasound; can assess the measurement of the flow rate of portal vein and direction of the flow rate in branch of the portal vein.

On endoscopy examination of esophageal varices; Grade 1- small size varices and no red color sign, easily compressible by endoscopy and the risk of bleeding within 2 years of their detection is less than 10%. Grade 2- varices are classified larger than grade one. Grade 3- varices are confluent and not compressible by endoscopy. Grades 4- large size with red spots develop and weakness of variceal wall or ruptured variceal wall [58].

Gastric varicesis classified bases on the location of the stomach and relation with esophageal varices [26]. Tensions (CSPH) are; present with esophageal or gastric variceal bleeding, ascites, hepartorenal syndrome, and hepatic encephalopathy. GOV- gastro-oesophageal varices are associated with esophageal varices. GOV1- varices are associated with lesser curvature of stomach. GOV2- varices are along with fundus of stomach. IGV- isolated gastric varices are isolated from the fundus of the stomach is IGV1, and ectopically in the stomach or duodenum is IGV2. The clinical signs of cirrhotic portal hypertension depend on severity of liver disease.

Cirrhotic portal hypertension is defined as an increase of pressure gradient between portal and systemic circulation. The most commonly parameter used to determine portal pressure is hepatic venous pressure gradient (HVPG) and commonly measuring pressure gradient between the portal vein and inferior vena cava [59]. In generally, hepatic venous pressure gradient is 1-5 mmHg. In compensated cirrhosis have 6 to 10 mmHg hepatic venous pressure gradient, while clinically significant portal hypertension develop when it more than 10 mmHg. Decompensated cirrhosis have more than 12 mmHg hepatic venous pressure gradient and manifested by the variceal rupture and bleeding, ascites, hepatic encephalopathy and development of portosystemic shunting [57-60]. Furthermore, more than 16 mmHg hepatic venous pressure gradient probability survival rate is below 70% and poor survival rate is associated with Child-Pugh class [61]. Furthermore, more than 16 mmHg hepatic venous pressure gradient probability survival rate is below 70% and poor survival rate is associated with Child-Pugh class [24-62]. The hepatic venous pressure gradient is a confirming quantitative assessment of portal hypertension. However there have other indicators of portal hypertension are; presence of variceal on endoscopic examination, on physical examination splenomegaly, ascites, ultrasound examination, computed tomography, magnetic resonance imaging studies.

All patients should be screening diagnosis for varices, when confirmed liver cirrhosis. However, may not compulsory in compensated cirrhosis patients as per Baveno IV, if transient elastoghraphy is less than 20 kpa or platelets count is more than 150×10^9 /L. Decompensated liver cirrhosis patients should have annual screening examination whether varices present or not present. Furthermore, compensated liver cirrhosis with varices patients can be screening examination every 1-2 years and compensated liver cirrhosis without varices can be screening examination every 2- 3 years [16-63].

Clinically significant portal hypertension: the step-wise diagnostic approach of portal hypertension, should be find out specific signs on physical examination such as spider nevi and visible abdominal portosystemic collaterals. If the absence of the physical signs on examination cannot be rule out clinically significant portal hypertension. The platelets count is the most common sign of the portal hypertension, it may correlated with hepatic venous pressure gradient and gastroesophageal varices. However, single diagnosis cannot accurate to either exclude or diagnosis of clinically significant portal hypertension or gastroesphageal varices. The platelets count can improve the noninvasive diagnosis of the clinically significant portal hypertension [64].

The ultrasound examination is safer, noninvasive, inexpensive, and provides the

morphological abnormality imaging that associated with cirrhotic portal hypertension. The presents of portal collaterals circulation on ultrasound examination, or computed tomography and magnetic resonance imaging or findings of the reversal flow within the portal system is 100% specific finding for clinically significant portal hypertension. The several other signs can detect on ultrasound examination such as dilatation of portal vein and reduction of portal vein velocity [65-67].

Clinically significant portal hypertension can be identified by noninvasive tests; lever stiffness more than 20-25 kilipascals (kPa), alone or combined with platelet count and spleen size [68, 69]. Hepatic venous pressure gradient more than 10 mmHg and liver stiffness more than 21 kpa are equally effective in predicting decompensated liver cirrhosis (57%).

Magnetic resonance elastiography is an emerging method to provided details of liver stiffness and spleen stiffness of much larger areas of the liver and spleen compared to ultrasound based techniques. Even MRI has been shown that accurate in staging of liver fibrosis.

Diagnosis of gastroesophageal varices: examining the presence with size of varices ans red wall markers require esophagealgastro-duodenoscopy (EGD). It is an invasive technique, discomfort during examination, and expensive examination that is not free of risks. Noninvasive examination is a preferable to determining the presence of high risk varices. So, as to circumstance is need for screening endoscopy. It is gold-standard examination for screening. If the esophageal varices are found on endoscopic examination, after then they are described as following: Grade I- collapse on inflation of the esophagus with air; Grade II- varices cannot be categorized as either Grade-I or Grade-III; Grade III- varices are larger to occulted more than 50 % of the lumen of esophagus.

5.1 Endoscopy:

Esophageal variceal bleeding is one of the most complications of cirrhotic portal hypertension. An appropriate early diagnosis of esophageal varices can minimized the high risk of bleeding from esophageal varices. Endoscopy is the gold-standard method for diagnosis of presence gastro-esophageal varices and find out signs of risks of bleeding in upper gastro-intestinal tract. Endoscopy screening examination recommended in all esophageal varices patients newly diagnosed with cirrhosis [63]. However, increasing the patients with early cirrhosis compensated advance chronic liver disease to achieve by non-invasive diagnosis methods, this strategy provide to large number of unnecessary endoscopy, which is decrease the patients compliance and increase the costs. In the last 10 years, non-invasive methods examination is increasing and provides the useful information about risk of varices, and treatment option for patients with compensated. Endoscopy remains to identify the other signs of cirrhotic portal hypertension such as esophageal varices, which is often the cause of severe bleeding in patients with cirrhosis.

5.2 Transnasal Endoscopy:

Transnasal small-caliber endoscopy performed without sedation and accuracy of lesion detection lower than conventional esophagealgastro-duodenoscopy and technique is much better tolerated, but cannot be used for variceal band ligation.

5.3 Capsule Endoscopy:

Capsule endoscopy is not currently sensitivity enough to replace esophago-gastro- duodenoscopy and grading of varices is not possible. It is not able to detection of fundus varieces and also not recommended for variceal screening and staging.

5.4 Transient Elastography:

Transient elastography is a noninvasive examination technique than can derive a value of tissue stiffness based on the speed of propagation of low-frequency ultrasound. It has been high sensitivity for detecting the severe portal hypertension, but is associated with a large variation in specificity [70]. Transient elastography use as a noninvasive tool for risk predication in patients with compensated advanced liver cirrhosis. The liver stiffness to spleen and platelet score (LSPS) had the highest discrimination factor such that a ratio of 2.65 was associated with a >80% risk of clinically significant portal hypertension. The amplitude and frequency of the initial stimulation are known by ultrasound and magnetic resonance imaging. It is possible to estimate the elasticity of tissues. The healthy liver is an elastic organ, while liver fibrosis increasing stiffness [71, 72]. It is the reasoning for use of elastography technique to estimate fibrosis. However, underlining any process occupying space in the liver tissues such as venous congestion, infiltrative neoplastic processes, inflammation and cholestasis, and meal ingestion increasing in liver stiffness that depends on liver fibrosis and it should be taken into account of interpretation of the elastiography results.

The ultrasound transient elastography has been first assessing to liver stiffness [73, 74]. It proved an accurate findings and ruling out of cirrhosis in patients with chronic liver disease [75, 76]. The values is more than 10 kPa suggested of advanced chronic liver disease and more than 12.5 kPa have an accuracy 90% in detected liver cirrhosis [77]. The liver fibrosis is the major component of hepatic resistant and it is major factor to leading portal hypertension in the liver cirrhosis patients with compensated cirrhosis. The liver stiffness test is a surrogate of portal pressure in liver cirrhosis patients. The liver stiffness can identified the clinically significant portal hypertension with high accuracy [78]. The values is more than 21 kPa the suggested of clinically significant portal hypertension [64-80], and it associated with high risk of clinical decompensated

cirrhosis and increasing high risk of hepatocelullar carcinoma [81]. The liver stiffness measurement is not an optimal method to identifying esophageal varices. However, the combination of values of liver stiffness measurement by transient elastography is less than 20 kPa with platelet count is more than 150×10^9 /L can be rule out larger varices in compensated liver cirrhosis patients. So, it is leading to reduce the number of the unnecessary endoscopies examination for esophageal varices [82].

The liver stiffness measurement cannot be used as a surrogate of the hepatic venous pressure gradient and are not correlated [83]. Moreover, liver stiffness measurement changes in the patients with non-selective beta-blocker but do not change in hepatic venous pressure gradient, and transient elastography cannot be used for monitoring of hemodynamic response to non-selective beta-blocker. Recently, in using newer ultrasound elastography that including point shear-wave elastography and two dimensional shear-wave elastography [73, 74]. It can allow to visualization in real-time them in area of elastic-wave velosisty and need to reliability criteria to base on quality of the ultrasound imaging. It is now considerate validated and provided as a higher capability for measurements of liver stiffness to compare transient elastography and with similarly accuracy of liver cirrhosis [84].

Magnetic resonance elastography method can evaluate both liver and spleen stiffness and it's over coming on the limitations of ultrasound transient elastography [85, 86]. It has been provide the accurate staging of liver fibrosis and highly promising for diagnosed cirrhosis in patients are not able to do ultrasound elastography [87, 88].

5.5 Radiological Findings in the Diagnosis of Cirrhotic Portal Hypertension

In the recently radiological imaging including ultrasound, endoscopy sonography, computed tomography, magnetic resonance imaging, angiography imaging and hepatic venous pressure gradient (HVPG), have been using the clinical evaluation of cirrhotic portal hypertension [5-12]. Among them ultrasound is the more advanced diagnosis for cirrhotic portal hypertension due to its noninvasive technique, accessibility, safety, nonionized method, locally available, affordable cost, real time ultrasound (RTUS), color Doppler ultrasound (CDUS), duplex Doppler ultrasound (dDU) and more convenient. Ultrasound examination for portal hypertension is clinically acceptable and reliable with accuracy; specificity and sensitivity are similar to other imaging mortalities [89-91]. Several morphological and hemodynamic ultrasound findings have been preferred as markers of cirrhotic portal hypertension.

Ultrasonography is the fist-line real time imaging examination for suspected cirrhotic portal hypertension patients. It is highly sensitivity in detected portal vein thrombosis and hepatic vein thrombosis, so it can able to corrected differential diagnosis in new case of cirrhosis and portal hypertension [92]. As for the limitation of ultrasound, internal observer variability, intestinal gas and obesity are major disadvantage of ultrasound. However, appropriated training and knowledge can markedly reduce it. Most of ultrasound signs have a high specificity and can able to considerate sufficient to confirm the diagnosis of cirrhosis and portal hypertension. Other hand, the ultrasound sensitivity of most of individual signs is low indicating that negative results so, cannot completely rule out compensated liver cirrhosis. The most accurate single sign found in early phases of liver cirrhosis that a nodularity on the liver surface [93, 94]. The combination of the nodular liver surface and portal vein mean velocity below the 12cm/sec holds an accuracy of 80% for discriminating between chronic hepatitis with severe fibrosis [95]. Most ultrasound signs are specific for portal hypertension, but their sensitivity are moderate especially in decompensated cirrhosis. The presence of ultrasound signs or a combination of signs is permits to confirm portal hypertension [66-96]. Porto-systemic collaterals and reversal flow in portal vein signs are 100% specificity for portal hypertension. Splenomegaly is more sensitivity than other signs for portal hypertention but less specificity. However, enlarged spleen is an independent predicator of gastroesophageal varies in compensated cirrhosis patients [64].

Other signs are dilatation of portal veinous system; reduce respiratory variations of splenic; and superior mesenteric vein diameter; reduced portal venous velocity; increased congestion index of the portal vein; and altered Doppler pattern in portal and hepatic vein. Less commonly explored signs are changes in the arterial flow of the hepatic, splenic, mesenteric and renal arteries. Most of these signs have correlation with the hepatic venous pressure gradient and none of them can use as reliable surrogate hemodynamic measurement, either as a first-line examination or after starting NSBB. Ultrasound parameters are indicated prognosis value or suggesting worsening of portal hypertension on follow up [66].

Liver cirrhosis usually combined with a coarse echo pattern parenchyma of liver on ultrasound examination and it reliable to signs in the determination of the liver cirrhosis [89-98]. Diagnostic accuracy of ultrasound for liver cirrhosis is more than 70 % [90]. Enlargement of spleen is more than 11cm, is one of valuable diagnostic sign with 80% diagnosis accuracy [99, 100]. Right lobe of the liver atrophy is usually associated with caudate lobe enlargement (101). Rapidly replaced hepatic inflammation in common courses of chronic hepatitis, and it lead to progression parenchyma fibrosis there after induce progressive hepatic morphological change with shrinkage liver and finally, resulting in liver surface nodularity [97-102]. The progression of liver fibrosis is gradual increase in portal

venous pressure and lead to progressive splenic and other splachnic venous congestion [99].

5.5.1 Portal Caliber:

Theoretically, portal hypertension leads to increase in inner dimension of main portal vein. However, it usually shown that main portal vein with portal calibers more than 13 mm suggested the portal hypertension with 100% specificity and an average 40% sensitivity due to portosystemic collateral shunt [103, 104]. The major finding is variation in the measurement of the main portal vein dimension owing to the patient's postural change, breathing and fasting [105]. Several physiological factors are including postprandial increase in splanchnic flow, respirophasic change, and patients positional change, it may cause size of variation in the portal vein after making this measurement diagnostically unreliable [65-106]. Archived a good ultrasonography determination of the diameter of the portal vein and advisable to place the transducer in the subxiphoid region. Using of the left lobe as acoustic window in sequencing to obtain an ultrasonography section on axis of the portal vein and there have no changes in the caliber of blood vessels during the breathing. A reduced variation in caliber of blood vessels during the breathing has been consideration specificity and sensitivity finding of portal hypertension.

5.5.2 Velocity and Direction of Portal Flow:

Portal velocity can be better advisable to use the right intercostals approach. For Doppler signal in depth visualization need to reduce the frequency emission to able to detected slow flow velocity or increasing high flow velocity. The frequency of emission of Doppler signal is a different parameter than pulse repetition frequency, and traditionally portal velocities are significantly slower in portal hypertension compare to normal person. It can diagnosis when the less than 15 cm/sec, with 88% sensitivity and 96% specificity [106].

5.5.3 Portal Hypertension and Thrombosis:

Cirrhotic portal hypertension has a high risk to developing thrombosis in portal vein compare to general population because of a slower portal flow velocity and clotting disorders it associated with hepatopathy. The color Doppler ultrasound is choice of diagnosis for portal hypertension and thrombosis. Additionally imaging mortalities are usually needed such as computed tomography angiography and magnetic resonance angiography.

5.5.4 Hepatic Artery:

According to compensatory mechanism the portal venous flow is reduced and hepatic arterial flow is increased [89-107]. Increased resistance index of the hepatic artery in the portal hypertension, this index is independent from the Doppler angle and only show the ratio between the end diastolic velocity and peak systolic velocity. The normal resistance index range from 0.5 to 0.7. The change in hepatic artery resistance has not extensively used to demonstrate cirrhosis and cirrhosis related portal hypertension.

5.5.5. Hepatic Vein and Suprahepatic Vein:

The color Doppler waveforms of hepatic veins in normal persons have triphasic morphology. These sequences are the central venous variation owing to the cardiac cycle there after blood flow runs forward the heart during the atrial and ventricular diastoles then briefly reverse during the atrial systole [108, 109]. Generally wave morphology are altered in 50% of the portal hypertension patients, dampened flow about in 30% and completely flattened flow in 20% [110]. The change in hepatic vein by thrombosis due to two major cause alteration hepatic vein flow in cirrhotic patients; first is regional blood flow acceleration resulting focal compression by regenerative nodules, and the second is dampening the normal pulsatile blood flow pattern by the fibrous tissues.

5.5.6. Slanchnic Vein:

Enlargement the superior mesenteric vein and splenic vein more than 1cm indicate portal hypertension. The lack of the caliber variation of splachnic vein during the breathing is highly sensitive and specificity for hypertension and some of the studies have suggested that the increased in diameter of splachnic vein during the inspiration less than or equally to 10% is indicated of portal hypertension [111, 112].

5.5.7 Spleen:

Enlargement of spleen is common finding in portal hypertension. However, it not considered a major finding because of enlargement of spleen can be seeing in varying of conditions such as lymphoma, amyloidosis, thalassemia and other diseases [113]. Generally absent of splenomegaly cannot be rule out cirrhotic portal hypertension. The splenic cranial-caudal axis measure is widely used method for size of spleen and it is consideration the enlargement when spleen size is more than 13 cm [113]. Enlargement of spleen is directed correlated with severity of cirrhotic portal hypertension and degree of presence esophageal varices [114]. The splenic rigidity can use transient elastography method, when predicating portal hypertension in cirrhotic patients [115]. Magnetic resonance imaging is choice of diagnosis and it appears low-signal intensity micronunodulars in all sequences [116]. Cirrhotic portal hypertension related enlargement of spleen usually seen small hyperechognic foci without acoustic shadow on the ultrasound examination. It can differentiate splenomegaly from other causes of enlargement of spleen [117].

5.5.8. Ascites:

Larger volume of fluids accumulation in abdominal cavity is a common finding of portal hypertension. However, it also not considered a major finding because of ascites can presence in varying of diseases such as nephrosis, pancreatitis, peritoneal

carinomatosis and other disease [118]. Origin of ascites fluid can define by imaging examination.

5.5.9. Portosystemic Collateral Vessels:

It is form of resistance of blood flow in portal system and increased resistance to flow in the small communicating channels between the portal circulation and systemic circulation. Development of portosystemic collateral is owing to regenerating new small blood vessels or blood flow reversion of veins with portal pressure gradient more than 10 mmHg [119]. Contrast enhancement computed tomography and magnetic resonance imaging are more sensitivity than ultrasonography examination for detect of systematic collaterals.

Gastroesophageal collaterals are form of coronary vein, short gastric vein and esophageal vein, and these vessels are well visualized by ultrasound. The coronary vein size is more than 6 mm in diameter and abnormal hepatofugal flow is indicating portal hypertension [120]. Coronary vein dilatation up to 6 mm diameter is seen in 26% in patients and 78% hepatofugal flow [121]. It divided into anterior and posterior branch and it supplying the esophageal and paraesophageaol veins. The variceal bleeding can depends on size of coronary vein and high risk of variceal bleeding [122].

5.5.10. Esophageal Varices:

It is venous dilations in the esophageal wall submucosa. The blood supply from the anterior branch of the coronary vein and drains in azygos or hemi-azygos.the prevalence of the esophageal varices in cirrhotic patient is 30 to 40 %. On the contrast enhancement CT and MRI can identify thickening of esophageal wall but, wall of esophageal thickening not easily detected on CT and MRI examination. However, the most patients need endoscopy examination to rule out of esophageal varices. More than 70% of esophageal varices patients occur variceal bleeding and within the 6 weeks after the variceal bleeding have 20% mortality in esophageal varices [122, 123].

5.5.11. Paraumbilicus Varices:

It origin from the left portal vein and connected with the superior mesenteric vein and inferior mesenteric vein, systemic circulation and around the umbilicus. The blood flow up to 5cm/sec in direction that detected in the ligamentum teres in normally and blood flow not extend anterior part of liver surface. However, hepatofugal venous flow in the ligamentum teres with velocity more than 5 cm/sec and blood flow visualized anterior surface of liver, which is highly specificity for portal hypertension [124].

5.5.12. Splenorenal and Gastrorenal:

The tortuous blood vessels are usually seen in the hilar region of the spleen and left kidney and they are connected with the splenic vein, coronary vein and short gastric vein and renal vein or adrenal vein. The tortuous of blood vessels are well visualized by enlarged spleen and ultrasound examination. Enlargement of renal vein can also be seen in renal tumor and arteriovenous malformation.

Severe portal hypertension is usually leading to portosystemic collateral including gastroesophageal veins, paraumbilical vein, splenorenal vein and gastrorenal vein [65-125]. These all collaterals are visualized and examination by real-time ultrasound except recanalization paraumbilical vein [91-126]. However, recanalization peraumbilical vein easily detected by color Doppler ultrasound with 70-83% sensitivity and more than 90% specificity [125-127]. Others collaterals including the pancreaticoduodenal vein, retroperitoneal veins, omental veins gallbladder varices and intrapelvic varices [128]. Gallbladder varices usually observed by color Doppler ultrasound and it additionally, especially useful in the evaluation of the portal vein thrombosis and cavernous transformation [129].

More than two decades, duplex Doppler ultrasound was widely used for portal vein velocity to evaluation of cirrhotic portal hypertension. The cirrhotic portal hypertension patients without collaterals were shown reduce mean portal velocity with 82-83% sensitivity, 80-96% specificity, and a reduced maximum portal velocity is 66% sensitivity, 98% specificity and diagnosis accuracy is 62.2% as compared with healthy persons [109-130]. When decreased mean portal velocity then result become increased intrahepatic resistance and increased hepatic venous portal gradient [131].

Varying types of radiological imaging diagnosis are available to provide better diagnosis, prognosis, and treatment planning for patients with cirrhotic portal hypertension. The catheter based on hepatic venography is the best one method to measurement of hepatic venous pressure gradient for severity of portal hypertension. However, catheter based on venography is not riskless method including infection, intravenous contrast reaction, loss of blood, and need sedation [79-132]. Non-invasive imaging mortality is offer to diagnosis of cirrhotic portal hypertension as supportive or complementary to catheter-based on venography. The contrast enhancement CT and MRI diagnostic methods provide excellent cross-sectional visualization of the portal venous system [79].

Computed tomography and magnetic resonance imaging can identify the full extent of the portal vein obstruction or thrombosis, portosystemic collaterals, clarify complex anatomy for treatment planning. CT scan examination is useful method to identify of gastric and esophageal varices. It has 90% sensitivity to determine esophageal varices and 87% sensitivity for gastric varices. However, CT scan has ionizing radiation and risk of allergic reaction and nephrotoxicity [133]. It can be detected signs of cirrhosis and identify prehepatic and

posthepatic cause of the portal hypertension, site and size of portosystemic collaterals pathways [134]. The scanning usually perform in the caudocranial direction from level of horizontal of the duodenum to the diaphragm with 5-8 collimation, 8-12 mm table speed, and delay scan of 60-70/s after the injected 100-120 ml contrast agent with flow rate of 2-3 ml/s. Magnetic resonance imaging has been using as an alternative examination method to the ultrasound for measurement of portal pressure parameters. It can be identified portosystemic collaterals pathway and concomitant of the liver disease without injected of contrast agent [135]. MR angiography is facilitated whole series of native bright blood on imaging.

Table 1: Hepatic venous pressure gradient correlated with clinical and advanced chronic liver disease

HVPG	Clinical end-points
Less than 5 mmHg	Normal
5 – 10 mmHg More than 6 mmHg	Mild portal hypertension Progression of chronic viral hepatitis High risk of recurrence after liver transplantation
More than 10 mmHg	Clinical significant portal hypertension Esophageal varices development Ascites Decompensation Hepatocellular occurrence
More than 12 mmHg	Esophageal variceal bleeding
More than 16 mmHg	High mortality
More than 20 mmHg	Failure to control bleeding
More than 22 mmHg	High mortality in severe alcoholic hepatitis

6. Management of the Cirrhotic Portal Hypertensive Variceal Bleeding

The treatment of varices and variceal bleeding can be stratified according to the clinical presentation and findings of radiological diagnosis of cirrhosis and portal hypertension. The objective of therapies for patients at an earlier stage is to prevention from development of the complications of cirrhosis and portal hypertension. Varices and variceal bleeding should be management in the context of the presence or absence of the complications of cirrhosis and cirrhotic portal hypertension, and compensated or decompensated status of the patient with varices and variceal bleeding should be selection of the different therapy. The compensated cirrhosis patients have ultimate options of therapy to prevent from decompensated cirrhosis and other complications of cirrhosis. In the compensated cirrhosis patients should be avoid etiological agent for correction of aggravating causes or substances, such as alcohol abuse, obesity, and avoid drugs that induces injury of liver tissues, can reduce or maintain portal pressure and reduces risk of decompensated condition.

Based on different type of treatment include: 1. Therapy for general liver disease- stop alcohol intake; 2. Therapy for viral hepatitis B or C by combination therapy; 3. Pharmacological therapy- non-selective beta blocker, vasodilators as nitrate, vasoconstrictors as terlipressin, somatostatin; 4. Use balloon tamponade; 5. Endoscopic therapy as sclerotherapy, endoscopic variceal ligation; 6. Endovascular intervention therapy as tansjugular intrahepatic portosystemic shunt, coronary gastric vein embolization or TIPS + GCVE; 7. Surgical treatment as liver transplantation.

The prevention from formation of varices and during the initial stage should be preventing from further complications of portal hypertension. Mostly use non-selective beta-blocker, nitrates, diuretics are administration, and low sodium diet. The treatment is monitoring with endoscopic examination, Doppler ultrasound, and hepatic venous pressure gradient (HVPG). The efficacy of treatment mortality is monitoring further investigation. While portal pressure is predicator of gastroesophageal varices formation and clinical importance of portosystemic collaterals as a predicator of severe complication so need to further investigation.

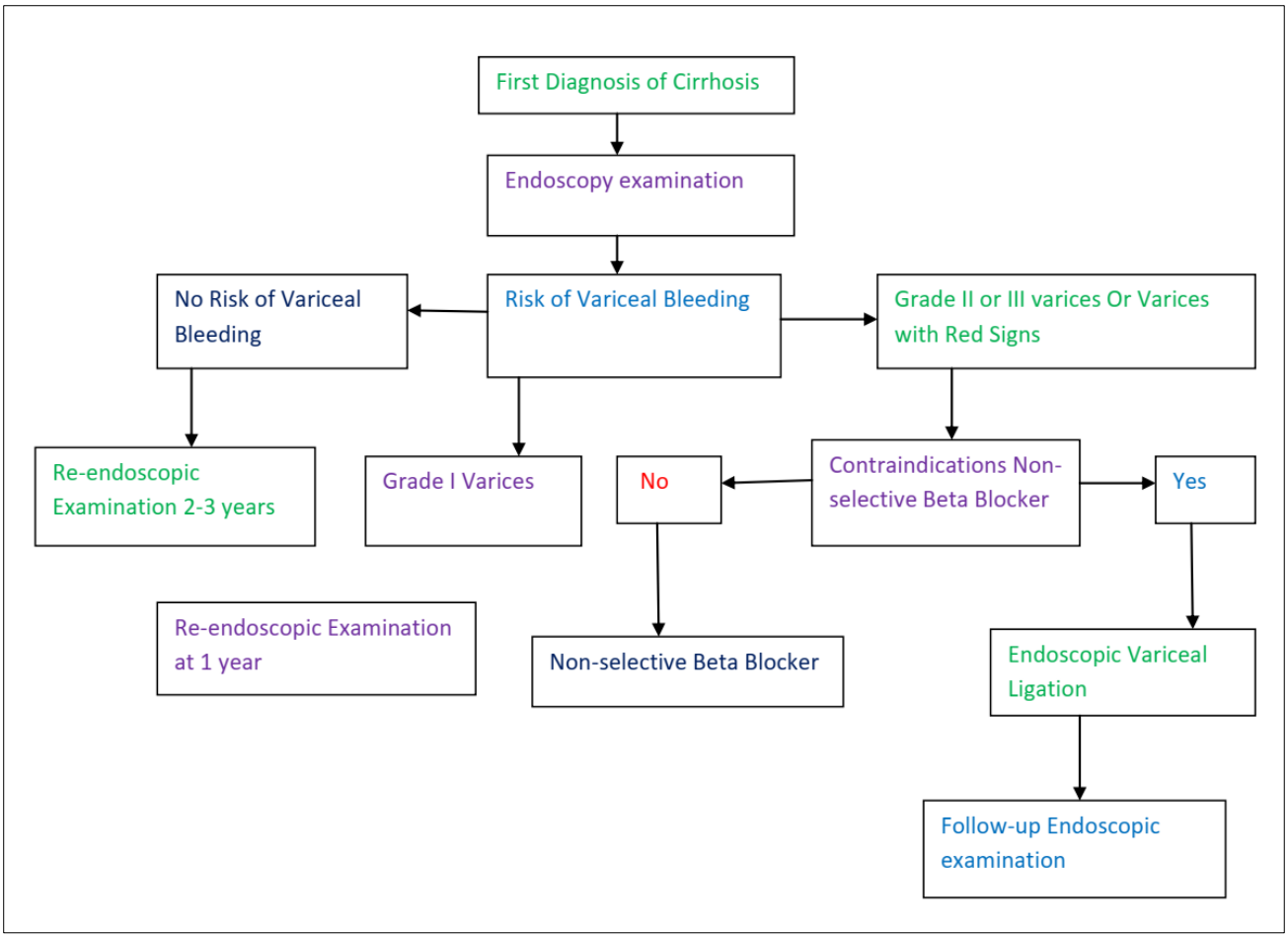

Figure 5: Flow Diagram of Algorithm for Primary Prophylaxis in Varices

6.1 Primary Prophylaxis:

Primary prophylactic management of patients at risk of variceal bleeding is a major goal of management of cirrhotic portal hypertension. First time diagnosed of liver cirrhosis patients should be done endoscopic screening examination for esophageal and gastric varices [136-138]. The endoscopic screening should be re-examination every 2-3 years in patients without diagnosis varices and every 1-2 years in those with grade-I or small varices [137]. Follow up of endoscopic examination should be related with the initial size of detected varices and in case of larger varices then follow up endoscopic examination is not necessary [137]. Since 30-50% of patients with cirrhotic portal hypertension occur variceal bleeding and about 20% patients die from the effected of the first variceal bleeding, so it seems rational to development prophylaxis regimens to prevent from variceal bleeding.

Patients with esophageal varices have risk of variceal bleeding is 30-35% within 2 years so, prophylactic treatment should be initiated on time [139]. High risk of variceal bleeding patients is usually associated with size of varices and red wall sign accompanied by Child-Pugh Class B or C. The primary prophylactic treatment can be reducing 50% risk of variceal bleeding [140]. While, lower risk of variceal bleeding patients not required primary prophylaxis treatment, there is not more effective to prevent further risk of bleeding in cirrhosis patients [10]. The treatment with a non-selective beta blocker is effectiveness in decrease the risk of the first variceal bleeding with larger or medium size varices [138-142].

The mainstay of the pharmacological therapy to the primary prophylactic of variceal bleeding has been non-selective beta blocker. The treatment options are available for primary prophylaxis of varices and variceal bleeding includes Non-selective beta blocker, endoscopic variceal ligation, and endoscopic sclerothepay. Non-selective beta blocker drug can be reducing the rate of variceal bleeding and related mortality. It can cause vasoconstrictor of the splanchnic venous circulation by beta-2 receptor inhibitor and reduced cardiac output by beta-1 receptor blocked. This result is in unopposed alpha-1 activity which is leading to decrease portal venous flow and portal pressure. Not all variceal bleeding patients are received beta blocker response with reduced of the hepatic venous pressure gradient [143]. More than 50% of beta blocker treated varices patients can archived reduction in hepatic venous pressure gradient below than 12 mmHg or more than 20% from baseline and it can play a role to prevent of

variceal bleeding [143, 144]. It can also decrease in azygos blood flow and decrease variceal pressure [144].

Propranolol and nadolol were introduced as a prophylactic management almost 4 decades ago [140-145]. Propranolol has been shown to reduce the portal pressure gradient, reduce of variceal venous pressure, and reduce azygos blood flow. In the recently years carvodilol is also effective and preferable drug for primary prophylactic to prevent of variceal bleeding. Carvedilol is a non-cardiac selective vasodilator beta blocker with mild intrinsic anti-alpha 1 adrenergic activity. It is more effective in lowering hepatic venous pressure gradient comparable than propranolol or nodolol plus nitrate and endoscopic variceal ligation [146-148]. It can reduce portosystemic collaterals resistance and hepatic stellate cells leads to a reduced intrahepatic venous resistance. The carvedilol can be greater reduction in portal pressure than propranolol, although reduce blood pressure [146-149]. The optimum dose of carvedilol is 6.25 to 12.25 mg per day [150]. Higher dose carvedilol is not recommended because of side effect, especially hypotension. It has significantly lower variceal bleeding compared with endoscopic variceal ligation, and also haemodynamic responders of carvedilol and propranolol have significantly lower mortality than treated with endoscopic variceal ligation.

Alternative option or contraindication of non-selective beta blocker for primary prophylactic management is endoscopic variceal ligation [151-154]. The previous three studies reported that there have no different between non-selective beta blocker and endoscopic variceal ligation in outcomes of primary prophylaxis management of variceal bleeding [153, 155]. Non-selective beta blockers are recommended as the first line therapy for primary prophylactic of variceal bleeding due to lowest costs, absence procedure related mortality and no need to expertise of endoscopist [140]. Endoscopic variceal ligation is recommended, when patients have intolerants or serious side effects and contraindication with non-selective beta blocker. Previous study suggesting that the non-selective beta blockers are beneficial in the compensated and early decompensated cirrhotic patients, but not beneficial for early liver cirrhosis and may be harmful in end-stage cirrhosis with refractory ascites [156].

Recommended doses for variceal Bleeding:

1. Propranolol 20-40 mg× PO × BD × a day.
2. Nadolol 20-40mg× PO × OD × a day.
3. Carvedilol 6.25 mg × a day (after 3 days increase to 6.5 mg × BD× daily and maintenance the maximum dose 12.25 mg after one week if tolerated or heart rate is < 50 -55 bpm).

For varices no effective therapy to prevent from development of varices and available prophylactic measures have disappointed with unacceptable side effects [157]. Small varices size can be enlarge rate of 12% at 1 year and 31% at 3 years [157]. Previous study showed that the nadolol result in slow progression to large varices 11% at 3 years as compare with placebo 37 % at 3 years, but there have no difference in mortality. Similarly, propranolol showing large varices 31% at 2 years as compared with placebo has 14% [157]. Patients have small varices with red wall signs or small varices with decompensated cirrhosis should be recommended non selective beta blocker therapy.

6.2 Acute Variceal Bleeding:

Acute variceal bleeding is typically present with painless hematemesis and recurrence. The variceal bleeding is more than two-thirds patients caused by liver cirrhosis [158]. The cirrhotic patients with sign of gastrointestinal bleeding should be treating as protocol of variceal bleeding until a definite diagnosis is made. Most studies are reported that the average 6 weeks mortality of the first episodes variceal bleed was up to 20% and in the hospital mortality was 40 -50%. About 40-50% of variceal bleeding cases spontaneously control without therapeutic intervention treatment [139-158]. More than the 80% of patients can be control of the acute variceal bleeding when using actual therapeutic moralities and in the remaining 20% of patients not possible to control acute variceal bleeding due to recurrence of bleeding in the first five days and first 6 weeks after initial bleeding episodes [158, 159]. About 30-40% of compensated liver function related esophageal in cirrhotic patients, while around 85% of decompensate have esophageal varices. The first episode esophageal variceal bleeding is occur about 10-15% at one year, and approximately 60% of cirrhotic patients are experience re-bleeding within 1 year without of proper treatment.

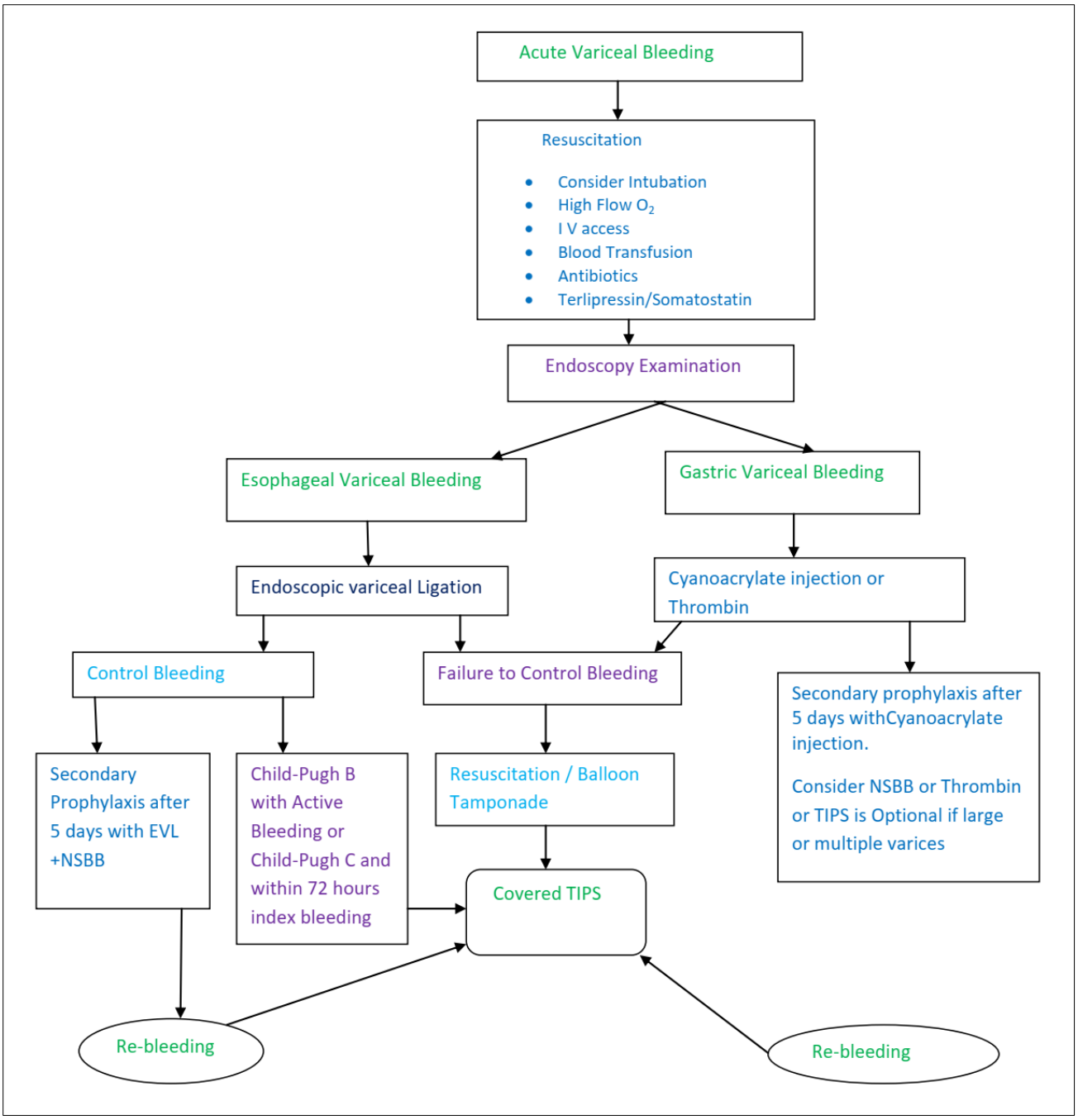

Figure 6: Algorithms for the Management of Acute Variceal Bleeding

The early mortality in patients with Child-Pugh class C, model for end-stage liver disease (MELD) more than 18, HVPG more than 20 mmHg, active bleeding on admission, portal vein thrombosis, and infection [25-161]. Previous study is reported that the correlation between the Child-Pugh score and hepatic venous pressure gradient such as 80 % of Child-Pugh C diagnosed patients have a hepatic venous pressure gradient is more than 20 mmHg [62]. Studies showed the HVPG, Child-Pugh score and MELD score to be stronger predicator for outcomes of cirrhotic portal hypertensive variceal bleeding [62-164]. These scoring are allow to referring patients to expertise specialist doctor for prevent from re-bleeding such as transjugular intrahepatic portosystemic shunt.

Most patients with a variceal bleeding are sufficiently stable. However, patients need to immediate goals of management for acute variceal bleeding are: (1) to decrease the risk of early re-bleeding; (2) to control the bleeding; (3) to prevent the bleeding related complications such as infection, acute kidney injury and hepatic encephalopathy.

Cirrhotic portal hypertensive patients with acute variceal bleeding are high risk of mortality owing to decompensated liver cirrhosis, coagulopathy,

encephalopathy and poor nutrition. Twenty percentage primary bacterial infections may occur in acute variceal bleeding and up to 50% of secondary infection.

Variceal bleeding requires to medical emergency management or intensive care unit by multidisciplinary-team approach involving the expertise specialist from emergency medicine, anesthesia, intensive care medicine, hepatologist and gastroenterologist, infection medicine, hepatologist, interventional radiologist and supportive teams. First should be assessment and protect airway and circulatory status. Resuscitation should be maintenance in order to haemodynamically stability and stomach should be evacuated by large bore gastric lavage tube. The transfusions of the blood for restore adequate blood volume and correction coagulopathy. In the acute variceal bleeding usually platelets count drop within 48 hours so need to transfusion platelets as necessary.

6.2.1 Resuscitation:

The clinical evaluation of the patients presented with variceal bleeding can be assessments are airway, breathing, and circulation. Most of patients are haemostatically stable with present, but those have severe bleeding or active recurrence bleeding they need to immediately resuscitation. In normally, two larger bore intravenous open, even central venous assess in certain cases. The patients need to regular monitoring pulse, BP, saturations until recovery. Tracheal intubation perform in those patients have high risk of aspiration with severe ongoing hematemesis. The choice of IV fluids for resuscitation can be used both crystalloid and colloid, while need for the transfusion of blood product assessed.

6.2.2 Transfusion Strategy:

For haemostatically stable patients, transfusion of the packed red blood cell must be restrictive with targeted haemoglobin level of 7-8 g/dL and this is usually assessed by either used laboratory samples or blood gas analyzer. Hepatic venous pressure gradient found to increase in patients with liberal transfusion but, there have remained the similar with those in the restricted transfusion. The restrictive transfusion strategy is only use to haemodynamically stable patients. In the chronic liver disease patients have an equal and opposite balance of pro-coagulant and anti-coagulant factors, so there have defaulting in interpretation of the clotting profile [165]. Thromboelastography is an available and quick point of care assay to assessment clot factors formation in whole blood, which gives more accurate guideline to use of prohemostatic factors [166]. Recently British Society Guideline recommendation that in the severe bleeding protocol, platelets is require to give when platelets count is blow than 50×10^9 /L and fresh frozen plasma when international normalized ratio is more than 1.5, and to give cryoprecipitate when fibrinogen below than 1.5 [20].

The commonly available treatment options are pharmacological treatment, endoscopic treatment, balloon tamponade, BRTO, TIPS procedure, TIPS combined GCVE and liver transplantation.

6.2.3 Pharmacological Treatment:

The aim of the pharmacological treatment in acute variceal bleeding to reduction of splanchnic blood flow and portal pressure [167]. Two type of vasoactive drugs using to control acute variceal bleeding are vasopressin or analogus drugs (with or without nitroglycerine) and somatostatin or its analogus drugs. In acute variceal bleeding single use vasoactive drugs can be achieved more than 80% hemostasis maintenance. Vasoactive drugs can be use when suspected variceal bleeding in cirrhotic portal hypertension patient, normally as soon as possible for prevent purpose, because approximately 25% of acute variceal bleeding patients die earlier after initial variceal bleeding [168]. Furthermore, if vasoactive drugs used before endoscopic therapy, it can reduce active bleeding during endoscopic therapy and increasing the success rate of endoscopic therapy [169, 170].

Table 2: Recommended doses for management of acute variceal bleeding

Drugs	Recommended Dose	Duration
Vasopressin	Continues intravenous infusion 0.2 to 0.4 U/ minuets or can be increase to 0.8 U/minuets × 24 hours, (it should always accompanied by IV nitroglycerin, starting dose of 40 µm/ minuet and can be increased to a maximum 400 µm/ minuet, for adjusted to maintain a systolic blood pressure 90 mmHg)	24 hours
Somatostatin	Starting IV bolus 250 µm (it can be repeated within one hour if ongoing continue bleeding) Continuous IV infusion of 250 -500 µm/h	2- 5 days
Octreotide (SMT Analogue)	Starting IV bolus 50 µm (it can be repeated within one hour if ongoing continue bleeding) Continuous IV infusion 50 µm	2- 5 days
Terlipressin (VP Analogue)	Starting 48 hours 2 mg IV every 4 hours until stop bleeding Maintenance with 1 mg IV every 4 hours for prevent re-bleeding	2-5 days

6.2.3.1. Vasopressin:

It is splanchnic vasoconstrictors that act on to reduce portal flow, portal pressure, portosystematic collaterals blood flow, and variceal pressure. Vasopressin drug can be control up to 60% patients with acute variceal bleeding, however it has limited efficacy to prevent from earlier re-bleeding and it does not improve long time survival [19-171]. It has a short half-life, so vasopressin applied continuously intravenous infusion. It is usually applied combined with nitrates to reduce adverse effect associated with vasoconstriction [172]. Vasopressin have significant systemic side effects are increase in peripheral resistance, reduction of cardiac output, heart rate, coronary blood flow, and systemic vasoconstriction with serious implication such as mesenteric or myocardial ischemia [173].

Vasopressin should be used in an intensive care setting due to the serious side effects, such as hypertension, breadycardia. It is usually administered as a bolus 0.4 unit, following by drip 0.4 to 1 unit /minuet, and combined with nitroglycerin to reduce portal pressure and counteracting systemic vasoconstriction.

6.2.3.2. Somatostatin:

It is cause splanchnic vasoconstriction and reduces portal pressure, portal blood flow, and hepatic venous pressure gradient [174, 175]. Trail studies are reported efficacy of somatostatin. It compares to placebo somatostatin, control of bleeding found 63% vs 46% respectively (169, 175). However, it is not beneficially for long term survival rate [139]. Somatostatin dose can give in starting bolus dose 250 µm thereafter following by 250 to 500 µm/hour continuous infusion 24 hours (176). High dose of somatostatin can be more effective in severe variceal bleeding [177]. It is effective over vasopressin in control of variceal bleeding and it better safety profile than vasopressin [178].

6.2.3.3 Octreotide:

It is a synthetic analogue of somatostatin with comparatively longer half-life. It not recommended single use in variceal bleeding, and usually used in combination with terlipressin. The ectreotide is more effective to prevent re-bleeding when it given additionally in endoscopic therapy [179]. It is administrated in starting bolus dose 25 µm, after then continue following by an infusion 25 to 50 µm/hour. The adverse effects of octreotide are abdominal cramps and mild hyperglycemia.

6.2.3.4. Terlipressin:

It is a synthetic analogue of vasopressin and it has an immediate systemic vasoconstrictor action. Terlipressin is dose of 2 mg intravenous every four hour, and can reduce the dose to 6 hourly, when can cause of peripheral vasoconstriction and manifestations painful hands and legs. The 5 days regimens of intravenous treatment have advocated in the Baveno V guidelines, while prorogated treatment of variceal bleeding has not been shown beneficial in long time survival.

6.2.4 Endoscopy Treatment:

The endoscopic diagnosis of variceal bleeding depending on presence of varices with white nipple sign and active bleeding. Endoscopy examination should be performed as soon as possible and not more than 12 hours after initial variceal bleeding presentation. The endoscopic optimal time is after sufficient resuscitation and pharmacological treatment, and it should be performed by a skilled endoscopic team, in an operating theater room with full anesthetic team, with available sufficient equipments and airway protection. During the endoscopic examination airway protection must be need because there have more chance to aspiration. It can reduce risk of aspiration if give prokinetic one hour before endoscopic examination such as metoclopramide, In order to help clean the stomach of clot blood [82].

During the initial endoscopic examination the location and size of varices should be carefully measured with in relation to the gastro-esophageal junction and details examination of the fundus of stomach for classified the gastric varices. Once confirmed the size and location of variceal bleeding thereafter perform variceal band ligation. Approximately 80 to 90% acute variceal bleeding is successfully controlling by endoscopic treatment [180]. Injection therapy is less commonly using recently, and it replaced by variceal band ligation (endoscopic variceal ligation). Sclerotherapy can cause local inflammation, local scaring, thrombosis and obliteration of blood vessels. Endoscopic band ligation is performing to use the transparent cap that attached to tip the endoscopic. The varice is pulled out by suction then rubber ring is thrown over the varices causing thrombosis and scaring of the vessel.

Before the introduction of variceal band ligation, aethoxysklerol injection was widely use in treatment of variceal bleeding. Sclerotherapy is effective compare with balloon tamponade [181]. Cyanocrylate injection is used as a second line treatment when failed variceal band ligation. Variceal band ligation is widely using and complications are less than sclerotherapy. The common complication of variceal band ligation is superficial ulceration and stricture of esophageal. Re-bleeding after variceal band ligation is less common. Disadvantage of variceal band ligation is impaired sight and coast compared to sclerotherapy is higher. Mortality rate of variceal band ligation is lower than sclerotherapy [182].

6.2.5 Balloon Tamponade:

Balloon tamponade is a lifesaving method in the cases of uncontrolled acute variceal bleeding than other methods of treatment. It is a more effective and can control approximately 90% of acute variceal bleeding.

However, re-bleeding can occur approximately 50%, when deflated the balloon tamponade [183].

Balloon tamponade can be occur severe complications such as esophageal necrosis, rupture of esophagus and aspiration pneumonia more than 15-20% of patients. If it appropriated place Sengstaken-Blakemore tube can be allow to safe transportation, resuscitation and even repeated endoscopic treatment or interventional radiology treatment. It should be placed under the direct vision use an endoscopic examination, especially when placed gastric balloon to confirm appropriated placed in the stomach. Esophageal balloon is rarely required to place and it only used when there is continuing variceal bleeding. In certainly conditions can be placed Sangstaken-Blakemore tube, inflated gastric balloon, when there is delayed in endoscopic and take chest X-ray to conform exact position before full inflated.

6.2.6 Self-Expandable Metal Stent:

It is using an alternative to balloon tamponade and it can insert without fluoroscopy, through endoscopic placed guidewire stent delivery (184). Self-expandable metal stent can easily removable and stent can be left in place up to 2 weeks. It can control variceal bleeding by compressed site of bleeding. This method is effectiveness to control of esophageal variceal bleeding and safe with minor complications such as necrosis, compression trachea and bronchial system and migrated stent [185, 186].

6.2.7 TIPS Combined with GCVE:

Transjugular intrahepatic portosystemic shunt is an established, minimally invasive procedure for treatment of the complications of cirrhotic portal hypertension such as an esophageal and gastric variceal bleeding and refractory ascites [187, 188]. TIPS can significantly reduce portal venous pressure through placement of artificial stent from portal vein to hepatic vein. Since the used of dedicated polyterafluoroethylene stent, patency of shunt has greatly improved (189). The first case of a TIPS using a bare-metallic stent on human was published in 1989 in a patient with Child-Pugh 'C' alcoholic cirrhosis with recurrent esophageal variceal bleeding [190]. However, the bare stent have poor prognosis with high shunt dysfunction, Pseudointimal hyperplasia and leakage of the bile duct transected in the lumen shunt [191-193]. Used expanded polyterafluoroethylene stent alone or combined with bare stent has become as the first line treatment. Compared with traditional surgical portosystemic shunt than transjugular intrahepatic portosystemic shunt is more advantages due to less invasiveness, less blood loss, better survival rate, using as rescue procedure and can performing under local anesthesia. It has been widely acceptable for treatment of cirrhotic portal hypertensive induce variceal bleeding, after first clinical successes application [187].

Transjugular intrahepatic portosystemic shunt has been recommended as the second line treatment option for cirrhotic portal hypertensive variceal bleeding based on the results of five meta-analyses and twelve randomized controlled trials [194]. Due to the rate of hepatic encephalopathy and shunt dysfunction was higher. However, previous randomized trial has reported that significantly survival benefit of earlier TIPS treatment with covered stent for variceal bleeding [195]. Notably, TIPS procedure can significantly decrease the level of the portal pressure gradient (PPG), but is only considered as the treatment choice after the failed first-line treatment [196]. Those patient have portal venous pressure ≥25 mmHg or high risk of the first line treatment failure and mortality, the primary goal is reduce the level of portal venous pressure, which indicate the apply TIPS as a first-line treatment for prevent further life threatening condition [197]. Earlier studies have reported that the TIPS combined with vericeal vein embolization are more effective for recurrent variceal bleeding and improve in liver function [198]. Gastric coronary vein embolization (GCVE) has been approved as an effective and supportive method for control the further more in esophageal and gastric variceal bleeding [199].

Before underwent TIPS+GCVE, all patients obtained contrast enhancement multiphase computed tomography (CT), contrast enhancement MRI, Ultrasonophraphy (USG), Liver function test, kidney function test, coagulation function test, routine blood test, history and physical examination , adequate monitoring records, history of hepatic encephalopathy, history of blood loss were reviewed and abdominal three-dimensional angiogram reconstructed computed tomography were obtained to determine the anatomic position of hepatic and portal veins. Child-Pugh class/score were calculated for known of severity of liver cirrhosis. The variceal bleeding patients received intravenous prophylaxis antibiotic before 30 minute start procedure. Simply, after routine disinfected with betadine solution (7.5% povidone-iodine) and local anesthesia (5ml lidocain 2%) injected in puncture side then right femoral artery was punctured with 18 G needle (seldinger technique) and 5F vascular sheath was introduced then through the sheath 5F catheter and 0.035 inch hydrophilic membrane guidewire introduced in to superior mesenteric artery for anteroposterior and lateral indirect portography to confirmed the shape of the portal vein. After then right internal jugular vein was punctured by the same method as an above and the 0.035 inch hydrophilic membrane guide wire and Rosch-Uchida transjugular liver access set (RUPS-100) were introduced into the right hepatic vein or middle hepatic vein, then left portal vein or right portal vein was punctured successfully after the angle of intrahepatic was adjusted. After then puncture needle was withdrawal and catheter and guide wire introduced into the distal or proximal end of splenic vein through the outer sheath tube then connected with high pressure syringe

angiography to evaluated the gastric coronary vein and collaterals veins. The angiography showed that the gastric coronary vein originated from the proximal or distal end of splenic vein or portal vein, diameter of collateral vein or variceal vain which was obviously thickened or curved and extended on the fundus of stomach or esophagus. After then pre-shunt, right atrial and portal venou pressure was measured. Then 5F snake catheter was applied for super selective angiography of gastric coronary vein and cook macro catheter was introduced through catheter into the variceal vain to embolization with different size of spring coil or cyanoacrylate (glue) + iodized oil. After embolized variceal vein then it was confirming by repeated angiography. After then amplatz guide wire introduced into parenchyma track and 6mm to 8mm × 6cm to 8cm balloon catheter was introduced through guide wire to dilated of intrahepatic track, then 7mm to 9mm × 4cm to 10cm stent (Luminexx + Fluency, Fluency, Viatorr, Astron, BARD, and Bare) was placed successfully between hepatic vein and portal vein and intrahepatic shunt was dilated with 4mm to 8mm × 4cm to 8cm balloon catheter. Stent position was confirmed by angiography and contrast medium flowed back into right atrium smoothly through the intrahepatic shunt. Post-shunt, atrial and portal pressured were measured then instruments was withdrawal and punctured site was blocked with starclose or exoseal or gauze pieces with bandage compressed.

Patients need to hospitalize till stable after TIPC+GCVE procedure and monitoring vital signs, abnormal pain, consciousness, GI bleeding and routine test. They were treated with analgesic, anti-coagulation drug, liver protection diet and strategies for prevention of hepatic encephalopathy. Patients informed and invited to enroll in the follow-up protocol with color Doppler ultrasound report, computed tomography angiography(CTA) report, liver function test (LFT), renal function test (RFT), blood coagulation function test, and blood ammonia Test at 1, 3, 6, and 12 months after the TIPS procedure and then every 6 months thereafter. TIPS related complications; re-bleeding, hepatic encephalopathy, shunt dysfunction, laboratory examination, portal vein pressure and death were recorded respectively. DSA examination was performing when Doppler Ultrasound and CT-scan suggested stenosis or occlusion in stent and patient come with chief complain of re-bleeding. Shunt dysfunction was recovered with balloon dilated of shunt channel and hepatic encephalopathy prevented with oral lactulose (15-30 ml × 3 times a day).

6.2.8. Liver Transplantation:

Liver transplantation is always one an option for acute variceal bleeding with severe decompensated cirrhotic portal hypertensive patients. However, rarely used or exceptional cases are can be treated. It is probably appropriated patients who bleed and awaiting on listed for transplantation. The liver transplantation is rarely option for most of the patients due to not commonly available and storages with delay in organ procurement. Still, there are not compared studies available about controlled trail of liver transplantation with uncontrolled or active variceal bleeding.

6.3. Secondary Prophylaxis Treatment for Variceal Bleeding:

The major goal of secondary prophylaxis is to prevent re-bleeding, whom the initial bleeding episode have successfully controlled, reduce further complications of liver cirrhosis and reduce mortality. The first episode of variceal bleeding patients has risk of re-bleeding approximately 60 % with a mortality rate up to 33 % [200].

6.3.1. Pharmacological Treatment:

The several previous studies are reported that the non-selective beta blockers propranolol or nadolol not effective for secondary prophylaxis after initial bleeding (139, 201-203). The portal pressure is reduction with carvedilol compare with propranolol. The compared variceal band ligation to non-selective beta blocker with nitrate is more effective than Variceal band ligation (204). One of the previous study reported that variceal band ligation to be advantage over non-selective beta blocker [205].

Nitrate:

The addition of isosorbide mononitrate and propranolol can be reduction of variceal bleeding compare with non-selective beta blocker alone and there was no survival benefit (206). Side effect of combined drug treatment group is more common drug withdrawal. The previous study reported that isosorbide mononitrate alone or with non-selective beta blocker or even variceal band ligation was no beneficial in mortality [207]. Isosorbide mononitrate single is not using in clinical practice due to certain side effect.

6.3.2. Endoscopic Treatment:

The variceal band ligation has preferred to treatment of variceal re-bleeding and it has lower rate of re-bleeding, mortality rate and complications than sclerotherapy [208]. In the sclerotherapy have ulceration rate is higher than variceal band ligation treatment. However, there have re-bleeding and mortality rate are similarly in both method [209]. The several previous studies are reported that sclerotherapy is effective in secondary prophylaxis treatment for re-bleeding [210, 211]. Sclerotherapy have replaced widely by variceal band ligation and an outcome of variceal band ligation is over on sclerotherapy [212, 213]. Pathophysiological point of view, variceal band ligation combined with non-selective beta blocker is more effective for secondary prophylaxis [214, 215]. Therefore, cannot be made at the moment clear recommendation of pharmacological treatment alone, variceal band ligation alone and combination treatment.

6.3.3. TIPS:

Transjugular intrahepatic portosystemic shunt is the recommendation for rescue therapy in patients with re-bleeding after controlled initial acute variceal bleeding despite combined therapies of non-selective beta blocker and endoscopic variceal ligation. The Patients who had treated with TIPS for acute variceal bleeding, they do not requiring specific therapy such as NSBB or VBL for reduce portal hypertension and variceal bleeding. However, in certain conditions should be referred for liver transplantation evaluation. Transjugular intrahepatic portosystemic shunt patency assessed by color Doppler ultrasound and computed tomography every 6 months. TIPS procedure is the treatment of choice in patient who had failed first-line treatment (NSBB+VBL) to control re-bleeding. Recently, TIPS with covered stent compared to VBL or glue injection plus NSBBs, results shown a significantly lower re-bleeding rate in patients treated with covered stent [216]. The previous one randomized controlled trail study reported that covered TIPS versus HVPG (propranolol+ isosorbid mononitrate), results showed lower re-bleeding rate in patients treated with covered stent TIPS and without differences in incidence of hepatic encephalopathy [217].

6.3.4. Surgery:

Liver transplantation can be considerate in severities of liver disease with variceal bleeding and it determined by the eligible patients selection criteria of country [218]. There was not clearly evidence still that prior shunt surgery have a significant outcome on liver transplantation [219]. The previous multicenter randomized controlled trails reported that the distal splenorenal shunt surgery compared with uncovered stent TIPS procedure, results showed similar re-bleeding and survival rate, however, shunt dysfunction and re-intervention was higher in uncovered stent TIPS [220]. Compared with traditional surgical portosystemic shunt with transjugular intrahepatic portosystemic shunt is more advantages due to less invasiveness, less blood loss, better survival rate, using as rescue procedure and can performing under local anesthesia. It has been widely acceptable for treatment of cirrhotic portal hypertensive induce variceal bleeding, after first clinical successes application [187].

7. Gastric Varices:

Gastric varices can be classified basis on the location of stomach with relationship in esophageal varices. It has implication for management of variceal bleeding. According to Sarin classification gastric varices are endoscopically classified: (1) gastroesophageal varices type I or GOV1 (lesser curvature) which is associated with esophageal varices and is most common gastric varices up to 70 %. (2) gastroesophageal type II or GOV2 (greater curvature) which is extend into on fundus of stomach. (3). Isolated gastric varices type I or IGV1 (fundus of stomach). (4). Isolated gastric varices type II or IGV2 (anywhere of the stomach except fundus of stomach) (26). Gastric varices are more commonly seen in the patients with cirrhotic portal hypertension due to portal vein and spleniv vain obstructions [26]. It can only occur 10-20 % in all variceal bleeding and its outcome is very worse than the esophageal varices [26-221]. The risk of re-bleeding is depends on the location of the varices and isolated gastric varices is highest risk of re-bleeding.

7.1. Management of Acute Gastric Variceal Bleeding:

The initial management of gastric varices bleeding is similarly to that of esophageal varices bleeding such as resuscitation, Vasoactive drugs, antibiotic, endoscopic therapy. If is the massive variceal bleeding then can be use balloon tamponade with Linton-Nachlas Tube as bridge to other treatments. After endoscopy examination the source of variceal bleeding identified then therapeutic options are include, endoscopic therapy, TIPS procedure, long term non-selective beta blocker.

7.1.1. Endoscopic Therapy:

The recently sclerotherapy has been widely replaced by variceal band ligation and adhesive or thrombin for gastric varice due to lower rate of re-bleeding and less complication. The previous three randomized controlled trails of meta-analysis reported that the cyanoacrylate injection compared with variceal band ligation, results showed that cyanoacrylate injection have significantly lower re-bleeding than VBL [222]. Several studies have showed the most commonly use of the cyaniacrylate for treatment of gastric variceal bleeding [223-225]. The one previous randomized controlled trail study comparing cyanoacrylate injection with variceal band ligation, the results are showed that treated with cyanoacrylate injection had a higher haemostasis rate, lowerre-bleeding and lower mortality than variceal band ligation [226]. Endoscopic variceal ligation is only prefer to small gastric variceal bleeding, which both the muvosal and contralateral wall of the vessels can be suctioned into the ligator. Endoscopic ultrasound guided insertion of coils and cyanoacrylate can be provided higher safety and efficacy for gastric variceal bleeding [227].

7.1.2 Transjugular Intrahepatic portosystemic Shunt:

The first-line treatment options for gastric varices are endoscopic variceal ligation and TIPS placement [228]. In clinical practice in the Western countries, TIPS is preferred as the first line treatment for gastric variceal bleeding, where as in East Asia, (South Korea and Japan) Bollon-occluded retrograde trancevenous is the treatment of choice [229]. Transjugular intrahepatic portosystemic shunt is more effective treatment for gastric variceal bleeding and more than a 90 % successfully rate in primary haemostatic [230]. In additionally emobolization is frequently required to portosystematic collaterals feeding varices. In the case of fundus of the stomach varices bleeding

have a higher chance early re-bleeding, Transjugular intrahepatic portosystemic shunt can be considerate as first-line treatment then other type of varices. TIPS treatment for either esophageal or gastric variceal bleeding, repotted similar re-bleeding after TIPS.

7.1.3. Balloon Occluded Retrograde Transvenous Obliteration:

BRTO is a procedure for fundal gastric variceal bleeding and it associated with larger gastrosplenorenal collaterals (231). In this procedure involves insertion of balloon catheter into outflow shunt via jugular or femoral vein. Blood flow is blocked by balloon inflation, after then the veins draining gastric varices are embolization with microcoils and seclerosant injection to obliterate varices [232, 233]. BRTO is the theoretically advantages over the Transjugular intrahepatic portalsystemic shunt that it does not diverted portal blood inflow from the liver. However, its variation can be increasing portal venous pressure and might be worse complications are increase ascites and it induce esophageal variceal bleeding. Several studies have suggested that BRTO is a better treatment option and it recently considerateas the treatment of choice for gastric varices bleeding, usually when patients with massive bleeding, re-bleeding [234, 235]. The previous study is reported that BRTO is superior in compare to TIPS due to improve liver function in gastric variceal bleeding patients [236].

8. CONCLUSION

Management of the variceal bleeding is common and often life threatening complication of cirrhotic portal hypertension. The more than three decades have markedly improving in the management of the cirrhotic portal hypertensive variceal bleeding due to the better overall care in the acute setting, updated treatment guidelines, specially use covered stent in TIPS, involves multidisciplinary expertise, and better understanding mechanism of portal hypertension. The best mortalities for prophylaxis and treatment of variceal bleeding due to the cirrhotic portal hypertension were reviewed in numerous of clinical studies and follow treatment guidelines.

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Cite this article: Gauri Mukhiya & Rumit Jha (2026). Management of Variceal Bleeding in Cirrhotic Portal Hypertension. *EAS J Anesthesiol Crit Care, 8*(1), 32-62.