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Updated Management and Prediction of Gastroesophageal Varices in Cirrhotic Patients

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Abstract

Background: Cirrhosis is a condition that result from chronic liver disease, and is characterized by advanced fibrosis, scarring, and formation of regenerative nodules leading to architectural distortion. Patients with cirrhosis are at increased risk of numerous complications that can occur secondary to portal hypertension, abnormal liver synthetic function, or combination of both. Portal hypertension (PH) is an increase in portal pressure beyond the threshold of 10 mmHg (clinically significant portal hypertension, CSPH) increases the risk of gastroesophageal varices (GEVs). Gastroesophageal varices (GEV) are the most relevant porto-systemic collaterals resulting from clinically significant portal hypertension, for which the presence of EV is an independent predictor of mortality. Variceal bleeding is one of the most fatal complications of portal hypertension which caused by rupture of gastric and mainly OV with a mortality rate of 17% to 57%. Non-invasive predication of varices in cirrhotic patients is useful as generalized screening of all cirrhotic patients by endoscopy would increase the work load of endoscopy units.

Keywords: Gastroesophageal Varices, Cirrhosis, Portal Hypertension.

Cirrhosis

Cirrhosis is anirreversible condition results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture. This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction **(1).**

Epidemiology:

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide, 170.000 per year in Europe, and 33.539 per year in the USA. Cirrhosis is the main indication for 5500 liver transplants each year in Europe **(2)**.

Evidence based studies showed that the burden of liver cirrhosis is growing in both the West and the East. The mortality rate due to cirrhosis in the Caribbean, Latin America, Asia, Oceania, Africa and Europe had increased significantly from 1980 to 2010. Egypt had the highest age-standardized mortality rate for cirrhosis, while Mexican had the greatest number of deaths in the

Latin Americans. In Asia, the highest incidence of liver cirrhosis was observed in Thailand **(3).**

Assessment of Liver Cirrhosis

- **Child-Pugh classification**

Currently, the most commonly used classification of liver function for patients with LC is Child-Pugh classification. This was originally designed to predict mortality during surgery in patients with LC **(4).**

Table (1): Child-Pugh score **(5).**

	Points		
Variable	**1**	**2**	**3**
Encephalopathy	None	grade I–II	grade III–IV
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>35	28–35	<28
Prothrombin time (seconds)	<4	4–6	>6
Sum of points	5–6	7–9	10–15
Stage	A	B	C
1-year survival rate (%)	95	80	44

The main limitations of the Child-Pugh score are the empirical cut-off values of laboratory parameters and the inclusion of clinical variables needing subjective assessment (ie, encephalopathy and ascites) **(6).**

- **The Model for End-Stage Liver Disease (MELD) score**

The Model for End-Stage Liver Disease (MELD) score was originally developed as a prognostic model of early mortality in LC patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) **(7).**

MELD score includes variables of serum concentrations of bilirubin and creatinine and international normalized ratio for prothrombin time (INR) and, in most liver transplantation centers, MELD score has replaced the Child-Pugh score for priority of organ allocation due to superiority of prognostic ability of MELD score **(7).** Recently MELD score is modified to include level of serum sodium.

Recent treatment of liver fibrosis and cirrhosis:

Current concepts of the pathogenesis of hepatic fibrosis demonstrate that liver fibrosis is a dynamic and reversible**(7).**

There are many suggested therapeutic strategies as the following:

- **Therapies to eliminate the cause:**

Treatment of the cause is considered the most direct and effective method. Treatments of viral hepatitis, stop alcohol abuse, weight loss and blood lipid control, iron and copper chelators are thought to be effective therapies **(8).**

- **Anti-inflammatory and immunosuppressive drugs:**

Injury of hepatocytes and motivation of HSCs occurs mainly due to inflammatory and immune response. Therefore, anti-inflammatory drugs and immune-suppressive can be used to hinder

fibrosis, especially for viral hepatitis, autoimmune hepatitis and primary sclerosing cholangitis. The anti-inflammatory drug like celecoxib, antioxidative agents and vitamin E can suppress fibrogenisis **(9)**

Glucocorticoids, azathioprine and colchicines provide anti-inflammatory, antifibrotic properties and immune-modulatory effects. Therefore, they are useful in the treatment of liver fibrosis **(10).**

- **Suppression of HSCs and promotion of apoptosis:**

HSC is considered the most critical cell in in hepatic fibrosis. Therefore, suppression of HSCs is an important therapeutic line. Particular cytokines and many growth factors eg: insulin-like growth factor-1, IFN-α and IFN-γ have been shown to promote apoptosis of HSCs and exert antifibrotic effect **(11).**

- **Promotion of hepatocyte regeneration:**

Hepatocyte apoptosis is an important cause of fibrosis and cirrhosis. Prevention of hepatocytes apoptosis and promotion of hepatocytes regeneration is a useful therapeutic strategy. Silymarin is considered useful hepatoprotective agent in the treatment of cirrhosis. Ursodeoxycholic acid and tauroursodeoxycholic can protect hepatocyte from injury and have been proved to be beneficial agents for the treatment of primary sclerosing cholangitis **(12).**

- **Targeted therapy and gene therapy:**

TGF-β, PDGF-β, CTGF, and TIMP are very important in pathogenesis of liver cirrhosis. Therefore, these genes have been studied as therapeutic targets for liver cirrhosis. Antisense oligo-nucleotides and small interfering RNAs (siRNAs) against these genes have been tested. SiRNAs are artificially synthesized double-stranded RNA. They are used in transient silencing of gene of interest **(13).**

MiRNA has been implicated in the pathogenesis of liver cirrhosis through regulation of profibrotic and antifibrotic genes, and control the proliferation and activation of HSCs. miRNA-based therapy can be beneficial in treatment of liver fibrosis **(13).**

Gastroesophageal Varices

Variceal bleeding is one of the most fatal complications of portal hypertension which caused by rupture of gastric and mainly OV with a mortality rate of 17% to 57% *(***14).**

Prevelance of gastroesophageal varices:

Oesophageal varices are present in about 40% of patients with Child–Pugh A cirrhosis and in 60% of decompensated patients (Child–Pugh B and C) **(14).**

The clinical course of compensated cirrhosis can be classified according to presence of esophagealvarices into compensated cirrhosis with absence of OV or presence of OV. There is significant morbidity and mortality rates in compensated cirrhotic patients with OV **(14).**

If patients are without varices, they develop them at a rate of 8% per year**(14).**

Normal venous drainage of esophagus:

Venous drainage of the esophagus can be divided into 3 parts:

- Venousdrainage from the upper two thirds of the esophagus enters the central venous circulation via the superior vena cava.
- The lower third is drained by the periesophageal plexus, this complex drains into the anterior branch of the left gastric vein (into the main left gastric vein) and enters the portal circulation at the splenic vein or directly into the portal vein**. (23).**

The vascular structure of the normal lower esophagus is complex, can be classified into intrinsic, extrinsic and venae comitants of the vagus nerve**(23).**

I- <u>Intrinsic veins of gastro esophageal junction: consist of:</u>

(1) ***Intraepithelial veins:*** They run radially within the esophageal epithelium and they are responsible for the endoscopic finding of red wale markings and cherry red spots in advanced esophageal varices.

(2) Sub epithelial veins: They are present in the lamina propria and drain without valves into sub mucosal group of veins; they freely communicate with their equivalents in the stomach

(3) Sub mucosal veins: They lie deep to muscularis mucosa. They enlarge to form tortuous channels in advanced liver cirrhosis

(4) Perforating veins: They arise from sub mucosal veins and perforate the muscular coat reaching the extrinsic veins; they are present in area above oesophagogastric junction **(24).**

The intrinsic veins of gastro esophageal junction are divided into four well defined zones:

- **Gastric zone:** a 2-3 cm zone with its upper end at esophageal junction and composed of radial band veins in submucosa and lamina propria.
- **Palisade zone:** this begins at esophagogastric junction and extends cranially for 2-3 cm and represents a direct extension ofveins of gastric zone, which runs in palisades of longitudinally arrayed veins in the lamina propria. These veins form the primary communication between the portal bed and azygos bed.
- **Perforating zone:** the intrinsic veins as mentioned before drain into extrinsic veins by way of valved perforating veins. In case of esophageal varices, they show bi-directional flow in the lower esophagus on Doppler ultrasonography.
- **Truncal zone:** this is an 8-10cm zone extend upwards from the perforating zone.

The blood in the intrinsic veins runs in cranial to caudal direction and drain via perforating veins into extrinsic veins **(25).**

II- Extrinsic veins:

They are embedded into the outer fibrous layer of esophagus close to the esophageal nerve plexus and drain into inferior thyroid, brachiocephalic veins in the neck, azygos vein in the thorax and the left gastric vein in the abdominal part of the esophagus **(26).**

III- Venae commitants of vagus nerve:

They begin caudally as branches of left gastric vein and run with gastric nerves in esophageal adventia to drain into azygos and hemiazygos veins **(27).**

The esophageal varices are supplied with blood mainly from the cardiac branch of left gastric vein through cardiac venous plexus **(27).**

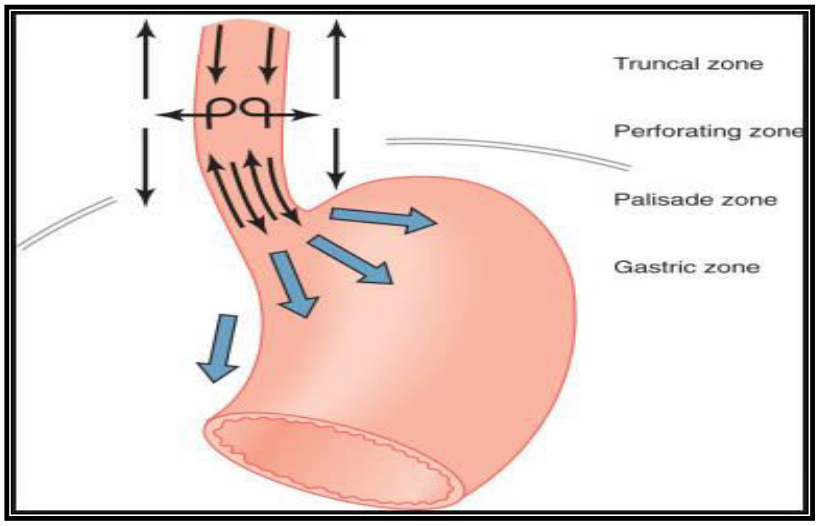

Fig. (1): The venous drainage of intramural portion of gastroesophageal varices including gastric, palisade, perforating and truncal veins **(28).**

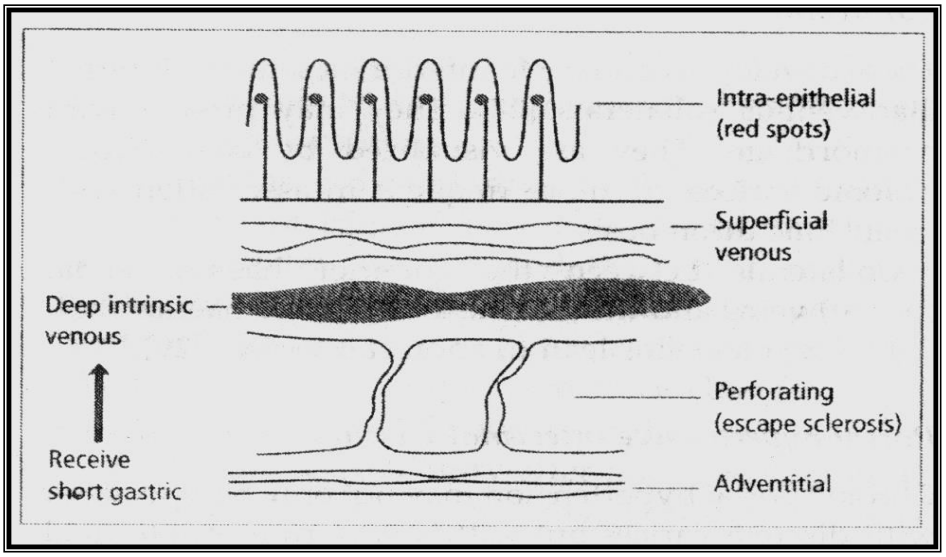

Figure (2): Venous anatomy of the oesophagus **(29).**

Mechanism of Variceal Hemorrhage:

In portal hypertension, 90% of the portal flow is diverted back to the heart through portosystemic collaterals. This is mediated by remodeling and enlargement of these vessels by VEGF, NO-driven VEGF type II receptor expression, and platelet-derived growth factor **(15)**.

Variceal rupture occurs when the wall tension becomes more than the elastic limits of the variceal wall. The wall tension is defined by Frank's modification of Laplace's law $T = (P_{varices} - P_{esophageal\ lumen}) \times$ (radius of varix)/wall thickness **(30)**.

Variceal pressure is dependent on variceal flow and resistance to outflow. Variceal flow is determined by the severity of portal hypertension. So, the major determinants of variceal hemorrhage are high portal pressure and the variceal diameter. The strongest predictor for development of varices in those with cirrhosis who have no varices at the time of initial endoscopic screening is an hepatic venous pressure gradient (HVPG)>10 mmHg **(16).**

Patients with an HVPG >20 mmHg are at a higher risk for early rebleeding (recurrent bleeding within the first week of admission) or failure to control bleeding (83% versus 29%) and a higher 1-year mortality (64% versus 20%) compared to those with lower pressure**.** (**31).**

Varices are more superficial at the gastroesophageal junction and thus have the thinnest wall in that region so, esophageal variceal hemorrhage usually occurs in this region **(32**).

Prediction and diagnosis of esophageal varices:

Non-invasive methods:

Non-invasive predication of varices in cirrhotic patients is useful as generalized screening of all cirrhotic patients by endoscopy would increase the work load of endoscopy units **(17).Laboratory tests:**

- **Platelet count (mm3)/spleen diameter (mm) (PC/SD)*:***

- It is the commonest parameter with a constant cutoff value (909) in most studies; it is calculated by dividing platelet count/ml³ by the maximum spleen bipolar diameter in cm measured by abdominal ultrasound.
- Thrombocytopenia, large spleen size, portal vein size and PC/SD can strongly predict big number of patients with O. Vtudies **(33).**

- **AST-to-platetlet ratio index (APRI):**

- It is a commonly used serum test and has been more extensively studied with cut off value 1.4 **(34)**.
- It is calculated by the following formula: [(AST/ULN) x 100]/platelet count 109/L (ULN = the

upper limit of normal) **(35).**

- **FIB-4:**

- This test is based on Platelet count, AST, ALT and age.
- FIB-4= [age (years) x AST (IU/L)] / [platelet count (109/L) x ALT (IU/L) 1/2]
- FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. **(36).**

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- **Blood ammonia levels:**

- There is strict correlation between ammonia levels and portal hypertension with portosystemic collateral channels that carry blood away from the portal venous system to the general circulation **(37).**

- **AST/ALT ratio :**

- It has sensitivity 71% and specificity56% at cut off value 1.1**(38).**

- **Combination of ALBI grade and platelet count (ALBI-PLT score**):

- The albumin-bilirubin (ALBI) ratio was used a good model for evaluation of hepatic functional reserve in patients with HCC to assess the priority in transplantation list **(39).**
- The score was calculated using the formula: −0.085× (albumin g/L) + 0.66×log (bilirubin μmol/L).
- The ALBI grades are classified into 3 grades, grade 1 (lowest mortality risk) (ALBI score ≤ -2.60), ALBI grade 2 (score -2.60 < and ≤1.39) (intermediate mortality risk) and grade 3 (score >-1.39) (highest mortality risk)**(39).**
- Thesegrades are added to a point equivalent to platelet count.One point was given to the platelet count >150,000/mm3 and 2 points were given to the platelet count ≤ 150,000 /mm3. **(39).**

- **Forns' index :**

- It is calculated according to the following formula: 3.131-7811 x ln [platelet count (109/L[(0.781 x ln[GGT(IU/L)] + 3.467 x ln [age (years)] – 0.014 [cholesterol (mg/dL)] **(40).**
- The cut off value s for prediction of OV is 8.5 **(34).**

1) Fibroindex:

The cut off value for prediction of clinically relevant OV is 2.5 and the index can be calculated by the following formula:

1.738 - 0.064(platelets [$\times 10^4$ /mm^3]) + 0.005(AST [IU/L]) + 0.463(gamma globulin [g/dl]) **(41).**

- **<u>Imaging techniques:</u>**

1) Plain radiographic findings:

Calcification may be seen in the portal vein after prolonged portal hypertension. The calcification is linear, and lies transversely across the upper abdomen, or it slopes upward and obliquely toward the liver hilum. In 5-8% of patients, O.V. may be seen as lobulated posterior mediastinal masses **(42).**

2) Ultrasound:

Ultrasound is a safe, cheap and can be repeated easily. It has higher specificity but lesser sensitivity as it is operator dependant **(43)**.

Inter-observer variability is considered a major drawback, but appropriate training and knowledge

markedly reduce it. Intestinal gas and obesity limit the exploration **(43)**.

In patients with clinical suspicion of cirrhosis the detection of nodular liver surface is an excellent non-invasive method to rule in cirrhosis, while the combination of ultrasound and TE allows the best diagnostic performance **(43)**.

Porto-systemic collaterals (e.g. paraumbilical vein, spleno renal collaterals, etc.) and reversal of flow in the portal vein are pathognomonic signs of portal hypertension. Splenomegaly is commonly associated with portal hypertension; this sign is more sensitive than other signs, but less specific as the size of the spleen is not well correlated with the level of portal hypertension; however, if splenomegaly is absent, portal hypertension is unlikely **(18).**

However, increasing spleen size is an independent predictor of gastroesophageal varices in compensated cirrhosis **(18).**

3) Doppler ultrasound:

Doppler ultrasound is also a non-invasive method. It estimates blood flow volume in portal circulation and it was widely used to explore the relationship between O.V. hemodynamics associated with portal hypertension and liver cirrhosis **(44).**

4) Elastography:

From a physical point of view, elasticity is defined as the ability of a tissue to maintain its shape after being challenged by a mechanical stress. This is an intrinsic characteristic of each tissue **(45).**

The application of a mechanical stimulus to any tissue, such as a vibration or an ultrasound impulse or sound waves, induces the formation of shear waves in this tissue. These waves propagate into the tissue with a velocity depending on the tissue elasticity **(46).**

There are three different elastography techniques that measure liver and spleen stiffness. Transient elastography (FibroScan) uses a mechanical wave generated by a special transducer, while acoustic radiation force impulse imaging (ARFI) and shear wave elastography (SWE) use sound waves (point SWE&2D SWE) **(47).**

Elastography techniques are commonly used for the evaluation of liver fibrosis and in the evaluation of portal hypertension **(19).**

Recently, the Baveno VI Consensus Conference recommended LSM values of 20–25 kPa as an accurate cutoff to identify patients with CSPH**;** in fact, patients with LSM values > 10 kPa at TE were considered suggestive of compensated advanced chronic liver disease (cACLD) and values of LSM≥ 21 kPa were defined to rule in CSPH **(48).**

TE has the low accuracy in obese patients (an extra-large XL probe is now available) and the over estimation of liver stiffness in patients with elevated ALT serum values **(19).**

Several studies have shown that the accuracy of p-SWE for the evaluation of liver fibrosis is comparable to that of TE**.** Similar to TE, p-SWE has been studied as a noninvasive tool to evaluate PH. However, studies published until now have reported conflicting results about the correlation of p-SWE and HVPG **(49).**

As expected, 2D-SWE performed as well as TE in assessing liver fibrosis with a higher accuracy in the diagnosis of mild and severe fibrosis and with a greater applicability**.** More recent, studies from different groups have reported a good correlation of 2D-SWEwith HVPG suggesting that it might be a useful tool in the a ssessment of PH **(39).**

5) Computed tomography (CT):

CT allows direct visualization of esophageal varices after intravenous contrast administration, as serpiginous vessels that protrude in the lumen of the lower esophagus. CT also depicts portosystemic shunts in the abdomen **(50).**

6) Magnetic resonance imaging (MRI):

CT is a superior imaging modality to MRI in the detection of esophageal varices. Furthermore, the evaluation of portal hypertension stigmata on imaging, such as paraesophageal, gastric and perigastric varices, recanalized peri-umbilical vein and spleno-renal shunt, did not improve the predictive value when compared to the presence of esophageal varices alone **(20).**

Table (2): Most commonly observed signs of cirrhosis on imaging ***(51).***

Observed signs of cirrhosis on imaging	
Liver morphology changes	♦ Nodular liver surface (all imaging methods, but better visualized by high-frequency probe on ultrasound). ♦ Coarse echopattern (ultrasound); heterogeneous density with nodular pattern in some cases (CT). ♦ Hypertrophy of the left lobe and atrophy of the segment IV (better visualized on CT and MRI); expanded gallbladder fossa (CT and MRI). ♦ Hypertrophy of caudate lobe. ♦ Reduction of the medial segment of left hepatic lobe.
Hepatic veins	♦ Narrowing and loss of normal plasticity of flow by Doppler. ♦ Altered straightness. ♦ Non-uniformity of hepatic vein-wall echogenicity.
Hepatic artery	♦ Increased diameter (all techniques) and tortuosity (CT).
Portal venous system	♦ Dilatation of portal vein (≥13 mm), splenic vein and superior mesenteric vein (≥11mm). ♦ Reduction of portal vein blood-flow velocity. ♦ Reversal of portal vein blood flow.
Spleen	♦ Increased size (splenomegaly: diameter >12cm by ultrasound).
Presence of porto-systemic collateral circulation	
Minimal perihepatic ascites	

Invasive Methods:

1. Measurement of HVPG:

HVPG is measured by introducing catheter through internal jugular, femoral or cubital vein under local anesthesia. Then the balloon catheter enters the hepatic vein. The hepatic venous outflow is

blocked by the inflation of the balloon and wedge hepatic venous pressure (pressure at the tip of catheter) equals hepatic sinusoidal pressure and portal venous pressure. Free hepatic venous pressure (FHVP) is measured by deflating the balloon near hepatic vein opening in inferior vena cava. HVPG is the pressure that the portal blood flow has to exceed to pass through the liver which equals difference between WHVP and FHVP **(44).**

Table (3):interpretation of measured hepatic venous pressure gradient (HVPG) **(51).**

HVPG	*Clinical end-points*
<5 mm Hg	***Normal***
5–10 mm Hg	***Mild portal hypertension*** ▪ Progression of chronic viral hepatitis. ▪ High risk of recurrence after liver transplantation.
>10 mm Hg	***Clinically significant portal hypertension*** ▪ Oesophageal varices development. ▪ Ascites. ▪ Decompensation. ▪ Hepatocellular occurrence. ▪ Decompensation after hepatic resection.
>12 mm Hg	***Oesophageal varices bleeding***
>16 mm Hg	***High mortality***
>20 mm Hg	***Failure to control bleeding***
>22 mm Hg	***High mortality in severe alcoholic hepatitis***

2. Upper GIT endoscopy:

Esophago-gastro-duodenoscopy (EGD) is the best method and the gold standard for diagnosis & grading of varices and detection of risk signs for bleeding (red signs) including:

- Red wale markings (dilated venules longitudinally seen on the variceal surface with appearance of a wale or whip mark)
- Cherry red spots (small red spotty dilated venules about 2 mm in diameter on the variceal surface)
- Hemocystic spots (large round red projections >4 mm in diameter looking like blood blister)
- Diffuse redness (diffuse red area seen on the variceal surface due to the development of telangectatic network) **(47).**

Diagnostic upper endoscopy was recommended in all cirrhotic patients till 2015 **(17).**

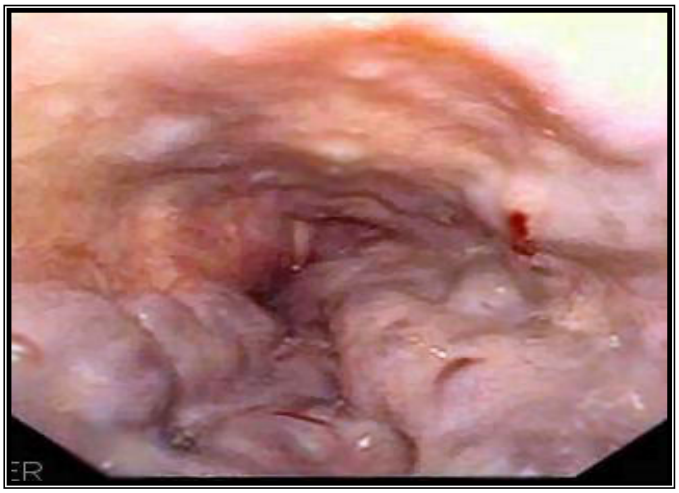

Fig (3): Endoscopic image of oesophageal varices with prominent cherry-red spots**(21).**

Prevention and treatment of gastroesophageal varices:

❖ **Primery prophylaxis:**

♦ **Prevention of first variceal hemorrhage in patients with medium or large varices (with or without risky signs):**

Pharmacological Prevention (nonselective β-blockers):

Use of NSBB ***(propranolol or nadolol)*** in prevention of first variceal hemorrhage was associated with a lower rate of first variceal hemorrhage. The 2-year rate of variceal hemorrhage is15% in NSBB users compared to 25% in non NSBB users***(52).***

Carvedilol has additional vasodilatory effect and may enhance reduction in portal pressure by decreasing intrahepatic resistance. It has been shown that the reduction in HVPG achieved with carvedilol is more than that with propranolol ***(52).***

Prevention by EVL (endoscopic variceal ligation):

Although NSBB is considered the standard in the prevention of first variceal hemorrhage, EVL appeared as an effective therapy **(Bosch et al., 2008).**

♦ ***Combination therapy:***

It is not recommended as it showed no difference in the rate of first variceal hemorrhage or death. In addition, a higher rate of side effects was noted **(22).**

According to EASL guidance 2016, the choice among the previous treatment options depends on experience, resources, contraindications and side effects and patient's preferences. It is useful to start with a non-invasive and least costly option. Therefore, first option is to start with a traditional NSBB (propranolol or nadolol) and, if not tolerated even at the lowest dose, carvedilol is the second option. If drug therapy is not tolerated, EVL should be considered **(22).**

There are many advantages of using a NSBB over EVL. The dose of NSBB should be adjusted to the maximum tolerated dose or to a target that heart rate 50-55 beats/min. NSBB may not only reduce the risk of variceal hemorrhage but also prevent decompensation **(22).**

Common side effects of NSBB include fatigue, weakness, hypotension, and shortness of breath **(48).**

Although EVL has fewer side effects compared to NSBB, adverse events of EVL are more severe and can lead to death when they occur. Some of these adverse events are bleeding, post band ulcerations, and adverse events associated with conscious sedation or anesthesia. Repeated EVL

sessions are needed until varices are obliterated. Recurrence of varices occurs in about 90% of patients, so surveillance endoscopies are important. The first surveillance endoscopy should be done in 1-3 months after variceal obliteration and then every 6-12 months**(41).**

- **Primary prophylaxis in patients with small varices:**

In patients with small varices that have risky signs (red wale signs) NSBB or carvedilol are recommended. Use of NSBB in patients with small varices without risky signs is optional to delay the progression of the low-risk varices **(53).**

- **Primary prophylaxis in Patients with cirrhosis and have no varices:**

A large multicenter trial concluded that no benefit of nonselective β-blockers usage in preventing the development of varices in patients with cirrhosis (with HVPG >5 mmHg) and had not developed varices**.** This patient should have a follow up endoscopy every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence). If decompensation occurs, endoscopy should be performed by the time of decompensation **(22).**

- **Treatment of patients presented with acute variceal hemorrhage:**

1. **General measures:** Volume restitution should be initiated to preserve tissue perfusion. Packed red blood cells transfusion should be done to maintain the target haemoglobin level between 7 and 8 g/ dl. Other factors such as cardiovascular disorders, age, hemodynamic status and ongoing bleeding should be considered **(40)**.
2. **Antibiotic prophylaxis:**Antibiotic prophylaxis should be initiated from admission in patients with cirrhosis presenting with upper gastrointestinal bleeding.Intravenous ceftriaxone 1 g/24 h should be given in patients with advanced cirrhosis in situations with high prevalence of quinolone-resistant bacterial infections like hospital admission and in patients on previous quinolone prophylaxis **(17).**
3. **Prevention of hepatic encephalopathy:** Recent EASL/ AASLD HE guidelines state that episodic HE should be treated with lactulose (25 ml q 12 h until 2–3 soft bowel movements are obtained, followed by dose reduction to maintain 2–3 soft bowel movements per day). Recent studies suggest that either lactulose or rifaximin may prevent hepatic encephalopathy in patients with cirrhosis and upper GI bleeding **(22).**

4. **Pharmacological treatment:** Vasoactive drugs should be started as early as possible, before endoscopy. Vasoactive drugs (terlipressin, somatostatin, octreotide) should be combined with endoscopic therapy and continued for up to five days. These drugs lower the portal pressure by vasoconstriction of the splanchnic vessels**(17). Endoscopy:** Patients with upper GI bleeding should undergo upper endoscopy within 12 h of presentation.Band ligation is the recommended endoscopic intervention for acute oesophageal variceal bleeding. Tissue adhesive (e.g. N-butylcyanoacrylate) is recommended for isolated gastric varices and gastroesophageal varices type 2 (GOV2) that extend beyond the cardia**(40)**.
5. **Early TIPS placement:** An early TIPS within 72 h (better <24 h) must be considered in patients withhigh risk of treatment failure (e.g. Child-Pugh class C <14 points or Child-Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy**(22)**.
6. **Balloon tamponade:** Balloon tamponade should only be used in refractory bleeding as a temporary bridge (maximum of 24 h) until definitive treatment can be done **(22)**.
7. **Use of self-expandable metal stents:** Self-expanding covered oesophageal metal stents may be effective in refractory oesophageal variceal bleeding as balloon tamponade with less side effects

(17).

Figure (4): Endoscopy image showing SEMS in esophagus; a feeding tube can be seen **(39).**

❖ **secondary prevention:**

♦ ***Patients who have recovered from an episode of variceal hemorrhage:***

The1-year risk of recurrence of variceal hemorrhage can be as high as 60%. **AASLD guidelines** recommendedcombination therapy (NSBB plus EVL) is in these patients and constitutes first-line therapy.

TIPS should be considered in patients who are Child A or B who suffer recurrent variceal hemorrhage despite combination therapy **(22).**

TIPS were found to be superior to the combination of endoscopic therapy with pharmacotherapy in preventing the rebleeding. This is accompanied by an increase in the risk of encephalopathy without early or late survival benefit **(22).**

Patients who performed TIPS during the acute episode do not require specific therapy for portal hypertension or varices but should be referred for transplant evaluation. TIPS patency should be assessed by Doppler ultrasound every 6 months **(22).**

♦ ***Secondary prophylaxis in patients with refractory ascites:***

NSBB (propranolol, nadolol) should be used cautiously in patients with refractory ascites with strict follow up of blood pressure, serum sodium and serum creatinine. NSBB should be stopped if the patient develops decrease in systolic blood pressure <90 mmHg, hyponatremia (<130 mEq/L) or acute kidney injury **(17).**

♦ ***Secondary prophylaxis in patients with portal hypertensive gastropathy (PHG):***

NSBB are first line in preventing recurrent bleeding from PHG. TIPS may be considered in patients with PHG who need repeated blood transfusion when NSBB and/or endoscopic therapies fail **(17).**

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