Recent Updates About Management of bleeding Gastroesophageal Varices in Cirrhotic Patients

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Abstract

Background: Cirrhosis is a heterogeneous disease with a high mortality, It is the fifth-leading cause of adult deaths and classified in to in two main prognostic stages: compensated and decompensated cirrhosis, depending on the presence or absence of clinically evident decompensating events (specifically ascites, VH, and encephalopathy. Gastro esophageal varices are present in approximately 50% of patients with cirrhosis, but this depends on the clinical stage. In patients with CC, GEVare present in 30%-40%, whereas they can be present in up to 85% of patients with decompensated cirrhosis. There are two approaches for treating GEV: primary prophylaxis to manage bleeding or emergency treatment for bleeding followed by secondary prophylaxis. Treatment methods can be classified into two categories: 1) Those used to decrease portal pressure, such as medication (i.e., nonselective β-blockers), radiological intervention [transjugular intrahepatic portosystemic shunt (TIPS)] or a surgical approach (i.e., portacaval shunt), and 2) Those used to obstruct GEV, such as endoscopy [endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), and tissue adhesive injection] or radiological intervention [balloon-occluded retrograde transvenous obliteration (BRTO)]. Clinicians should choose a treatment method based on an understanding of its efficacy and limitations.

Keywords: Cirrhosis, bleeding, Gastroesophageal Varices.

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Cirrhosis is a heterogeneous disease with a high mortality, It is the fifth-leading cause of adult deaths and classified in to in two main prognostic stages: compensated and decompensated cirrhosis, depending on the presence or absence of clinically evident decompensating events (specifically ascites, VH, and encephalopathy **(1)**

PH is the initial and main consequence of cirrhosis and is responsible for the majority of its complications ,Portal pressure (PP) which determined by the hepatic venous pressure gradient (HVPG), is used for prediction the development of complications of in patients with cirrhosis and chronic liver disease (CLD) without cirrhosis more than liver biopsy. **(2)**

Patients with advanced CLD may develop PH before the anatomical diagnosis of cirrhosis so patients with compensated cirrhosis and advanced liver fibrosis with HVPG >5 mm are considered c ACLD. **(3).**

The Child-Turcotte-Pugh (CTP) classification is used for classification patients with cirrhosis, Patients with cirrhosis belonging to the classA are compensated, whereas those in the B and C class are mostly decompensate, there are several stages have been recognized Based on PP, patients with CC can be divided into those with mild PH (HVPG>5 but<10mm Hg) and those with clinically significant portal hypertension (CSPH), defined by an HVPG >10 mmHg

CSPH is found in approximately 50%-60% of patients with CC without gastroesophageal varices **(4).**

Patients with GEV have an HVPG of at least 10mm Hg so Patients with GEV have by definition CSPH which increased risk of developing postsurgical decompensation, hepatocellular carcinoma (HCC)and overt clinical decompensation (ascites, VH, and HE) **(5).**

The staging of cirrhosis affect the treatment of PH because prognosis and mechanisms of disease and therapeutic targets are differenet ,Serum albumin and the Model for End-Stage Liver Disease (MELD) score are also independent predictors of decompensation, so cirrhosis should be described and stratified in two different clinical stages compensated and decompensated, defined by the presence or absence of overt clinical complications of cirrhosis (ascites, VH, and HE) and Patients with compensated cirrhosis should be sub staged into those with mild PH and those with CSPH which predicts the development of more-advanced stages, there are two sub stages are recognized among patients with CSPH, based on the absence or presence of GEV. **(1)**

Epidemiology:

Gastro esophageal varices are present in approximately 50% of patients with cirrhosis, but this depends on the clinical stage. In patients with CC, GEVare present in 30%-40%, whereas they can be present in up to 85% of patients with decompensated cirrhosis **(6)**

In patients with CC, varices develop at a rate of 7%-8% per year **(4)** and progression from small to large varices occurs at a rate of 10%-12% per year, with decompensated cirrhosis being an independent predictor of progression **(7).**

Pathophysiology:

Increasing intra hepatic resistance to portal flow due to vascular distortion from regenerative nodules and micro thrombi is the main cause of portal hypertension that reduce NO bioavailability leads to endothelial dysfunction and increasing intra hepatic resistance so using statins which has anti fibrotic properties may be helpful here.

PH is leads to formation of portosystemic collaterals that develop through the coronary and Short gastric veins which constitute GEV, splanchnic vasodilatation occurs before the development of the collaterals so the portal flow is entirely diverted through also release of NO cause splanchnic vasodilatation together with Hyperglucagonemia and neoangiogenesis leads to persistant portal hypertension **(8)**

Sodium and water retention caused by systemic vasodilatation leads to increasing blood volume and increased cardiac output ,also release of norepinephrine, angiotensin-2, and antidiuretic hormone leads to intrahepatic vasoconstriction, drugs like non-selective beta-blockers (NSBBs; propranolol, nadolol, and carvedilol), vasopressin (VP), and its analogue, terlipressin, and somatostatin (SMT) and its analogues (octreotide, vapreotide) used in the treatment of varices and VH by causing Splanchnic vasoconstriction but liver function will not improve. **(9)**

Diagnosis and Monitoring:

PH is defined as mild PH (HVPG>5 but<10mm Hg) and as CSPH (HVPG>10mmHG) In which all the complications of PH are more likely to appear (varices, clinical decompensation),HVPG is the difference between the wedged (or occluded) hepatic venous pressure and the free hepatic venous pressure this can be measured by catheterization of the hepatic vein by using balloon catheter, Normal HVPG is 3-5mm Hg, HVPG more than 5 mm Hg identifies patients with cACLD/CC secondary to conditions associated with sinusoidal hypertension **(4)**

HVPG>12mm Hg identifies bleeding risk In patients with GEV mostly because there is clear evidence that shows that reducing the HVPG to levels of 12mm Hg or below is associated with protection from variceal hemorrhage (VH) **(10)**

HVPG>16mm Hg indicates a higher risk of death and HVPG more than 20mm Hg predicts failure to control bleeding, early rebleeding, and death during acute VH **(11)**

1- Diagnosis of clinically significant portal hypertension by using Non invasive tests:

Pelvi -abdominal US provides safe and inexpensive imaging evidence of PH , Sonographic signs of PH have been described, such as dilatation of portal vein , reduction of portal vein velocity, recanalized paraumbilical vein, spontaneous splenorenal circulation,dilated left and short gastric veins **(12)**

The presence of portocollateral circulation and the reversal of flow within the portal system is 100% specific for CSPH and is sufficient for diagnosis , also Several imaging techniques can be used like computed tomography (CT)and magnetic resonance imaging **(13)**

The ability to assess liver stiffness by using elastography (TE; Fibro Scan) is now very important technique ,it has been shown that an LSPS (liver stiffness [in kPa] * spleen size [in cm]/platelet count [in number/ m m3] score)>2.06 was 90% specific in ruling in CSPH with a positive predictive value of >90%. **(12)**

Magnetic resonance elastography (MRE) is an emerging technique that provides data on LS and SS of much larger areas of the liver and spleen compared to ultrasound-based techniques Although MRE has been shown to be accurate in the staging of liver fibrosis data regarding its diagnostic performance in the diagnosis of CSPH are still very limited **(14).**

2- Using Noninvasive tests in diagnosis of GEV:

Baveno VI criteria can be safely used to avoid endoscopy because according to it and extended Baveno VI criteria, patients with an LSM <20kpa and platelet count >150,000/mm3 have a very low probability (<5%) of having high-risk varices **(3).**

Also it is used for excluding unaffected patients more than identification of high risk patients who needs treatment this leads to decrease in the number of surveillance endoscopy procedures by 30% **(14)**

ESGE recommends that patients with decompensated ACLD (liver stiffness measurement by transient elastography ≥20 kpa or platelet count ≤150×109/L) should be screened by upper GI endoscopy to identify high risk esophagogastric varices (esophageal varices that are medium or large in size or small-sizede sophageal varices with red wale markings and all must be documented in the endoscopy report ,on the other hand does not recommend video capsule endoscopy (VCE) for screening of esophageal varices **(15).**

In patients with cirrhosis secondary to hepatitis B, an LSPS (liver stiffness [in kPa]* spleen size [in cm]/ platelet count [in number/mm3] score) <3.5 was accurate in ruling out high-risk varices ,In patients who do not meet these criteria, screening endoscopy for the diagnosis of GEV is recommended when the diagnosis of cirrhosis is made **(16)**

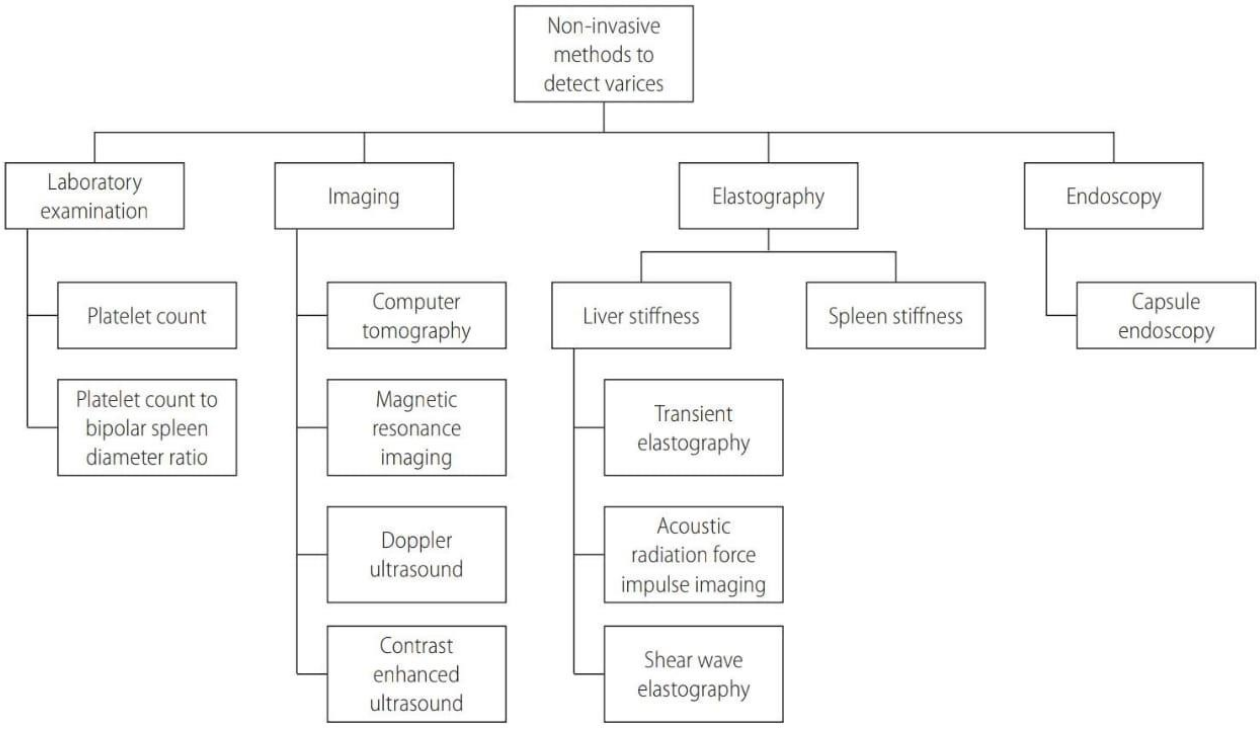
3-Monitoring the development of clinically significant portal hypertension and high-risk varices:

Endoscopy should be repeated every two years if there is active liver injury (active drinking in alcoholics and lack of SVR in HCV) but if there is small varices on screening endoscopy repeated endoscopy should be repeated yearly also during performing screening for HCC any evidence of worsening PH like appearance of new portosystemic collaterals in Imaging should be observed this has been associated with variceal formation and growth **(12)**

Patients with compensated ACLD (due to viruses, alcohol and/ornon obese [BMI<30kg/m2] nonalcoholic steatohepatitis) and clinically significant portal hypertension(HVPG>10mmHgand/or liver stiffness by transient elastography>25kPa) should receive ,if no contraindications NSBB therapy (preferably carvedilol)to prevent the development of variceal bleeding according to ESGE guidelines **(15).**

Varices can be uniformly described according to the general rules for recording endoscopic findings of EGV proposed by the Japan Society for Portal Hypertension **(17)**.

Non-invasive methods for detection of esophagogastric varices (**18)**



Sarin's classification of gastric varices: (19).

A- GOV: Gastric varices are continuous with esophageal varices

- **Type 1 GOV**: Extend 2–5 cm below the gastroesophageal junction along the lesser curve of the stomach Mildly tortuous.
- **Type 2 GOV**: Extend beyond the gastroesophageal junction into the fundus of the stomach and along the greater curve of the stomach Long, nodular, and tortuous

B- IGV: Gastric varices in the absence of esophageal varices

- **Type 1 IGV**: fundal varices Located in the fundus and fall short of the cardia by a few centimeters Nodular and tortuous often with red color signs
- **Type 2 IGV**:isolated ectopic varices Located in the body, antrum, or pylorus

4-Monitoring Changes in Hepatic Venous Pressure Gradient:

Decrease in HVPG to less than 12mm Hg is significantly reduces the risk of recurrent hemorrhage, ascites, encephalopathy, and death in patients with a history of VH but In patients with CC, reductions in HVPG >10% from baseline have been associated with a reduction in development of varices , first VH, and death **.(20)**

Management

According to the different clinical stages of cirrhosis and PH, therapy of varices and VH would be different, we aim to treat the patients at an early stage is to prevent the development of complications, varices and VH should be managed according to the status (compensated or decompensated) and the presence (or absence) of other complications of cirrhosis/PH (e.g., ascites, encephalopathy) **(21).**

A) Patients with compensated cirrhosis and mild portal hypertension:

This stage is defined by an HVPG >5 but<10mm and patients in this stage do not have varices or other complications of PH Elimination of the etiologic agent is the current mainstay of therapy because the main mechanism leading to PH is increasing the intrahepatic resistance so goal of therapy is to prevent development of CSPH also therapy has to be directed toward the etiology of cirrhosis. Antifibrotic drugs like Statins have proved to have lower incidence of decompensation (ascites and VH) In patients with compensated HCV cirrhosis and lower mortality by decreasing hepatic fibrogenesis, improving intrahepatic endothelial dysfunction, reducing PP, and improving liver perfusion and liver function **(11)**

B) Patients with Compensated Cirrhosis and Clinically Significant Portal Hypertension without Gastroesophageal Varices:

CSPH is defined as HVPG more than 10 mmHg so decrease in HVPG >10% from baseline associated with decreased risk of clinical outcomes , in this stage the main objective of treatment should no longer be to prevent varices, but to prevent clinical decompensation ,there is no role of NSBBs in preventing formation of varices. **(4)**

C) Patients with Compensated Cirrhosis and Gastroesophageal Varices:

GEV at this stage have been seen by endoscope, by definition they have CSPH, because the lowest HVPG in these patients is 10-12mm Hg the main objective is to prevent the first episode of VH reduction in HVPG to less than 12 mmHg by using NSBBs. **(22)**.

In patients at a high risk of bleeding like patients with medium/large varices or patients with small varices with red wale signs also decompensated patients with small varices, primary prophylaxis of VH is indicated (81)

Prevention of First Variceal Hemorrhage in Patients With Medium/ Large Esophageal Varices:

The primary pharmacological approach for prevention is the use of nonselective beta-blockers like propranolol or nadolol. These medications reduce the pressure in the portal vein, which helps decrease the risk of bleeding from varices. **(22)**.

Disadvantages of NSBBs are that approximately 15% of patients may have absolute or relative contraindications to therapy, and another 15% require dose reduction or discontinuation attributed to common side effects (e.g., fatigue, weakness, and shortness of breath. **(23)**

Management of patients with moderate /large varices that have not Bleed: (1)

Prevention of First Variceal Hemorrhage in Patients With Small Esophageal Varices

While small varices have a lower risk of bleeding compared to larger ones, some patients with small varices and risk factors may benefit from pharmacological therapy to reduce the risk of progression. This therapy typically involves the use of nonselective beta-blockers like propranolol or carvedilol**. (24)**

D) Patients presenting with acute esophageal variceal haemorrhage:

The immediate goal of therapy in these patients is to control bleeding, to prevent early recurrence (within 5 days) and prevent 6-week mortality **(3).**

Careful intravascular volume replacement by using crystalloid fluids if there is hemodynamic instability to restore tissue perfusion is mandatory, also transfusion/volume expansion in the individual patient should take into account other factors, such as age, cardiovascular disorders, ongoing hemorrhage and hemodynamic status **.(20)**

ESGE recommend that packed red blood cell (PRBC) transfusion strategy to initiate PRBC transfusion at a hemoglobin threshold of 7g/dL and maintaining it at 7-9g/dL) in hemodynamically stable patients with acute UGIB without history of cardiovascular disease and a "liberal" transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 8g/ dL hemodynamically stable patients history of cardiovascular disease **(15).**

Correction of the international normalized ratio (INR) by the use of fresh frozen plasma or factor VIIa is not recommended, because INR is not a reliable indicator of coagulation status in cirrhosis **(10)**

The use of antibiotic prophylaxis has been used to a decrease the development of infections, recurrent hemorrhage, and death because Patients with cirrhosis presenting with GI hemorrhage are at a high risk of developing bacterial infections. **(25)**

Intravenous ceftriaxone has been shown to be more effective in preventing infection compared to oral norfloxacin , this is explained by a high rate of infections by quinolone-resistant organisms ,Therefore the antibiotic of choice is intravenous ceftriaxone at a dose of 1g every 24 hours, duration of antibiotic prophylaxis is short term, for a maximum of 7 days it is the first choice in patients with advanced cirrhosis ,those who on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections. **(3).**

The use of vasoactive agents in acute VH is associated with lower 7-day all-cause mortality and lower transfusion requirements, the three most utilized worldwide are (SMT, octreotide, and terlipressin) all of them are used by intra venous infusion for 5 days depending on control of bleeding, following successful endoscopic hemostasis vasoactive agents may be stopped 24–48 hours later in selected patients Generally there is no significant differences among them, although terlipressin was used at doses lower than recommended **(26)**

The use of Octreotide leads to improve the overall control of acute haemorrhage, endoscopy must be done as soon as possible and not more than 12 hours after presentation, If a variceal source is confirmed, EVL should be performed provided the patient has been hemodynamically resuscitated **(27).**

ESGE recommends that endoscopic evaluation should takes place within 12 hours from the time of patient presentation after resuscitation also recommends in the absence of contraindications, intravenous erythromycin 250 mg may be given 30–120 minutes prior to upper GI endoscopy **(15).**

The routine use of proton pump inhibitors (PPIs) is no longer preferred according to recent guidelines despite using them decrease the risk of post EBL ulcer bleeding and reduce ulcer size, using them has been associated with an increasing the risk of bacterial infection, especially spontaneous bacterial peritonitis and infections caused by multidrug-resistant bacteria but if initiated before endoscopy, it should be discontinued **(7)**

Up to 20% of VH episodes can be refractory to standard therapy and are associated with a high mortality so "bridge" therapy may be necessary in order to acute control of hemorrhage until a more definitive therapy or a second session of endoscopy therapy can be performed, also Balloon tamponade is still used as bridge therapy and provides hemostasis in up to 80% of patients **(1)**

In patients at high risk of failure or rebleeding (CTP class C cirrhosis or CTP class B with active bleeding on endoscopy) who have no contraindications for TIPS, an "early" (preemptive) TIPS within 72 hours from EGD/ EVL may benefit selected patients and Patients who have a TIPS placed successfully during the acute episode intravenous vasoactive drugs can be discontinued and do not require NSBBs or EVL after recovery but should be assessed by Doppler ultrasound every 6 months**.(1)**

Patients who recover from the first episode of VH have a high rebleeding risk (60% in the first year), with a mortality of up to 33%. Combination of NSBB+EVL is first-line therapy in the prevention of rebleeding **(28)**

Hepatic encephalopathy is common in patients with cirrhosis and its prevalence increases during GI bleeding due to increasing ammonia production from blood protein digestion, liver failure, systemic inflammation, and infection .Hepatic encephalopathy at the time of admission during GI bleeding negatively impacts outcome and is independently associated with mortality **(28)**

Treatment of hepatic encephalopathy by Oral lactulose and/or lactulose enema patients with GI bleeding and concomitant hepatic encephalopathy improve the survival by rapid removal of nitrogenous waste products **(3).**

Although other ammonium-lowering strategies (e.g. L-ornithine, L-aspartate, and rifaximin) have been suggested to be as effective as lactulose in preventing the development of hepatic encephalopathy in patients with GI bleeding **(29)**

Drug	Recommended Dose	Duration
Terlipressin	Initial 48 hours: 2mg IV every 4 hours until control of bleeding Maintenance: 1mg IV every 4 hours to prevent rebleeding	2-5 days
Vasopressin	Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min It should always be accompanied by IV nitroglycerin at a starting dose of 40mg/min, which can be increased to a maximum of 400mg/min, adjusted to maintain a systolic blood pressure 90mm Hg	24 hours
Octreotide (SMT analogue	Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 50mg/h	2-5 days
SMT	Initial IV bolus 250mg (can be repeated in the first hour if ongoing bleeding) Continuous IV infusion of 250-500mg/h	2-5 days

E. Gastric Varices

Gastric varices (GV) are present in around 20% of patients with cirrhosis Cardiofundal varices are much more frequent in patients with portal vein and/or splenic vein thrombosis and Sarin's classification is the most commonly used for risk stratification and management of GV, GOV type 1 (GOV1) are EV extending below the cardia into the lesser curvature and are the most common (75% of GV). GOV type 2 (GOV2) are those extending into the fundus, Isolated GV type 1 (IGV1) are located in the fundus (IGV1), GOV2 and IGV1 are commonly referred to as "cardiofundal varices." Isolated GV type 2 (IGV2) are located elsewhere in the stomach **(30)**

Their localization (IGV1>GOV2>GOV1), large size, presence of red spots, and severity of liver dysfunction are factors that increase the risk of bleeding. **(16)**

For prevention of first VH from GOV2 or IGV1 may follow the recommendations for EV, NSBBs can be used although the data are not as strong as for EV, neither TIPS nor BRTO are recommended to prevent first hemorrhage in patients with fundal varices that have not bled **(22)**.

In patients with refractory ascites or SBP, high doses of NSBBs should be avoided. NSBB dose should be reduced or discontinued in patients with refractory ascites with signs of severe circulatory dysfunction, such as severe hypotension (systolic blood pressure<90mm Hg), hyponatremia (serum sodium<130 meq/L), or unexplained deterioration in renal function **(3).**

Management of acute hemorrhage from gastricvarices:

The initial treatment of gastric VH is similar to that of esophageal VH (volume resuscitation, vasoactive drugs, and antibiotics before diagnostic endoscopy, in case of massive bleeding, balloon tamponade with the Linton-Nachlas tube may serve as a bridge to other treatments. If using the Sengstaken-Blakemore or Minnesota tubes, inflation of only the gastric balloon and anchoring it against the gastroesophageal junction could be sufficient to produce adequate tamponade **(31).**

Urgent upper endoscopy is essential to identify the source of bleeding, assess the size and location of gastric varices, and perform endoscopic hemostasis procedures like banding, sclerotherapy, cyanoacrylate injection (glue therapy) is assosciated with lower rebleeding rates. **(31)**

In addition, EVL should only be performed on small GV in which both the mucosal and contralateral wall of the vessel can be suctioned into the ligator; otherwise, the band will fall off in several days, leaving an ulcer overlying the vessel, which can result in catastrophic re bleeding endoscopic ultrasound– guided insertion of coils and cyanoacrylatemay provide far greater safety and efficacy **(32)**

EUS-guide d injection therapy by cyanoacrylate should be decided on a case-by case basis and limited to centers with expertise in this endoscopic technique according to ESGE guidelines **(15).**

Prevention of re bleeding:

In patients who have recovered from cardiofundal variceal haemorrhage (GOV2,IGV1), ESGE recommends an individualized approach for secondary prophylaxis based up on patient factors and local expertise because there is lack of definitive high level evidence regarding specific eradication therapies(e.g. endoscopic cyanoacrylate injection ±NSBB,EUS guided injection of coils plus cyanoacrylate ,TIPS ,or BRTO)and appropriate treatment intervals **(15)**

The combination of NSBBs and endoscopic variceal therapy (EVL or cyanoacrylate injection) is the first-line therapy to prevent rebleeding and repeated cyanoacrylate injection is used more than NSBB in the prevention of rebleeding and mortality in patients with cardiofundal varices also it is an option for cases in which TIPS or BRTO are not technically feasible, but it is not appr oved for the treatment of GV **(33)**

F. Ectopic Varices:

The management of ectopic varices requires a thorough knowledge of the vascular supply to the varices , localization and anatomy are very heterogeneous which makes treatment becomes difficult, on the other hand diagnosis can be made with a contrast-enhanced CT in the portal venous phase, using large-volume diluted water-soluble oral contrast , the most frequent locations are surgical stomas, duodenum, jejuno-ileum, and colon, bleeding from ectopic varices is very rare in cirrhosis, but it is a significant source of bleeding in patients with pre hepatic PH **(34)**

Treatment options include endoscopic therapy, mostly with cyanoacrylate injection or endosonographic coil placement, TIPS with or without collateral embolization, and BRTO. In the case of stomal varices, direct injection of sclerosant agents or cyanoacrylateunder radiographic guidance can be very successful **(35)**

Prevention of rebleeding in patients experiencing the first variceal hemorrhage while on primary prophylaxis with nonselective beta-blockers or endoscopic variceal ligation:

Patients who bleed while on primary prophylaxis may need more-aggressive therapy, such as TIPS because rebleeding and mortality were significantly higher in patients who had bled while on prophylactic NSBBs compared to those that experienced VH not having been on NSBBs so Patients failing primary prophylaxis for VH may be treated with the combination of NSBBs and EVL or alternatively with TIPS **(36)**

Prevention and treatment of variceal haemorrhage in patients with hepatocellular carcinoma:

The risk of bleeding and prognosis of the bleeding episode might be worse in these patients (146) so these patients should receive the same secondary prophylaxis like the patients without HCC, including those who have PVT (tumoral or bland) the lack of secondary prophylaxis in patients with HCC recovering from acute VH is associated with high mortality **(37)**

Patients with refractory ascites or after spontaneous bacterial peritonitis:

Treatment with NSBBs in Refractory ascites and SBP are not absolute contraindicated , in these patients, high doses of NSBBs (over 160mg/day of propranolol or over 80mg/day of nadolol) should be avoided, given that they might be associated with worse outcomes**(38)**

NSBB dose should be reduced or discontinued in patients with refractory ascites with signs of severe circulatory dysfunction, such as severe hypotension (systolic blood pressure<90mm Hg), hyponatremia

(serum sodium<130 meq/L), or unexplained deterioration in renal function and after correction of renal function/ circulatory state may be used again to prevent recurrent He **(3)**

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