Brief Overview about Esophageal varices Management and Prevention

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Abstract

Background: Esophageal varices (EV) are the major complication of portal hypertension. It is detected in about 50% of cirrhotic patients, and approximately 5–15% of cirrhotic patients show newly formed varices or worsening of varices every year. It is a hemodynamic abnormality characterized by sudden bleeding episode, about a third of all patients with esophageal varices show bleeding episode. Inspite that both injection sclerotherapy and variceal band ligation are effective in controlling the acute variceal bleeding, band ligation is better for the initial control of bleeding and is accompanied with less side effects and improved mortality. Prevention of complications should run simultaneously to haemostatic therapies from admission of patients with cirrhosis and acute GI bleeding. The main complications, whatever the cause of bleeding, include bacterial infections (such as aspiration pneumonia or spontaneous bacterial peritonitis(SBP)), hepatic encephalopathy and deterioration of renal function. Bacterial infections are observed in more than50% of patients and may already be present at the time of bleeding (20%) acting as a precipitating event. Early TIPSS (before onset of treatment failure) within 72 hours of admission is associated with significantly lower mortality and treatment failure Shunt surgery reserved mainly for Child-Pugh A patients who has been shown to be an effective option as salvage treatment for patients where there is failure to control bleeding with VBL and vasopressors.

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Introduction:

Esophageal varices (EV) are the major complication of portal hypertension. It is detected in about 50% of cirrhotic patients, and approximately 5–15% of cirrhotic patients show newly formed varices or worsening of varices every year. It is a hemodynamic abnormality characterized by sudden bleeding episode, about a third of all patients with esophageal varices show bleeding episode (M. Merli, G et al., 2013).

(EV) are dilated collateral blood vessels that developed as a complication of PHT , gastroesophageal area is the main site of formation of varices. (EV) are formed when the hepatic venous pressure gradient (HVPG) exceeds10mmHg **(Garcia- Tsao et al., 2015).**

A key objective in managing the cirrhotic patients having varices is the primary prevention of bleeding. Either nonselective β-blockers or endoscopic variceal ligation is the treatments of choice for the primary prevention of variceal bleeding, Patients who survive an episode of variceal bleeding are at high risk for rebleeding. Combination of β- blockers and band ligation is the preferred therapy to reduce rebleeding rate. Failures of medical treatment should be managed aggressively with transjugular intrahepatic portosystemic shunting (TIPS), preferably using expanded polytetrafluoroethylene (ePTFE) covered stents **(R. De Franchis and M. Primignani 2011).** Because of higher rates of morbidity and mortality, rescue derivative surgery should only be considered in low-risk patients. Optimal management of esophageal varices requires a clear understanding of the pathophysiology and natural history. **(Sanyal AJ et al,.2008)**

Prevention and Management of esophageal varices:

1-Pre-primary prophylaxis:

Pre-primary prophylaxis denotes treatments to prevent the formation of varices. many studies were designed to evaluate the benefits of lowering the portal pressure in these patients using non-selective β blockers (NSBBs) and their role in preventing the formation of varices. In a large A randomized controlled trial (RCT) established that NSBBs are ineffective in preventing varices in patients with cirrhosis and portal hypertension **(Groszmann et al., 2005),** in another study, 213 patients with cirrhosis and PHT(minimum HVPG 6mmHg) were randomized to receive timolol versus placebo and the primary end-point was the development of varices or variceal haemorrhage. The mean follow-up was 54.9 months, with annual HVPG and EGD. The rate of primary end-point was essentially the same for the timolol group 39% and placebo 40%. Neither was there a significant difference in the rates of ascites, encephalopathy, transplant or death. However, the rate of serious adverse events was significantly greater in the timolol group (18%) vs placebo (6%). The strongest predictor for the development of varices was a HVPG of >10mmHg **(Haq and Tripathi, 2017).**

These studies prove that there is no pharmacological therapy effective enough to prevent the development of varices. Prevention of varices is no longer a satisfactory endpoint, and has been substituted by prevention of decompensation, liver transplantation and death **(De Franchis, 2015).** Patients with no varices need no treatment for portal hypertension but may benefit from therapies directed to stop fibrosis/cirrhosis progression by suppressing/interrupting the etiologic factor **(Marcellin et al., 2013)** e.g. HCV, HBV, alcohol, obesity, Fe, Cu. **(De Franchis, 2015, Garcia-Tsao G et al., 2017).**

Future patients with liver cirrhosis may also benefit from more or less specific antifibrotic drugs that are currently being assessed in randomized controlled trials (RCTs) (e.g. simtuzumab, obeticholic acid, statins, AT1 receptor-antagonists) **(Abraldes J et al., 2014).** The same concept

applies to compensated patients with small varices without red color signs (RCS) **(Garcia-Tsao G et al., 2017).**

2-Primary prophylaxis:

The aim at this stage is to slow the progression of varices and prevent first attack of variceal bleeding. (NSBBs) are the current mainstay of therapy in the prevention of first episode variceal hemorrhage. β1 inhibition reduces cardiac output while β2-blockade induces splanchnic vasoconstriction and together it results in decreased portal flow and pressure **(Thalheimer U et al., 2011).** Carvedilol has recently been investigated in portal hypertension given its alpha-blocking component and its potential to better diminish portal pressure, it is recommended to start at a low dose and to titrate up as tolerated until heart rate of 55 beats/minute is achieved (**Bosch, 2010).**

Baveno VI recommend NSBBs (Propranolol, nadolol, carvedilol) valid first line for small varices with red-signs or Child C, also it recommend either NSBBs or variceal band ligation (VBL) for Medium or large varices, Choice based on local resources/expertise or patient choice **(De Franchis, 2015).**

British Society of Gastroenterology (BSG) recommended primary prophylaxis for grade I varices with red-signs or grade II–III,by propranolol 40 mgbid, nadolol 40mg od or carvedilol6.25mg od titrated to 12.5mg od aiming for resting heart rate 50–55 bpm also it recommended that no need for surveillance EGD once NSBBs started, if NSBBs contraindicated or patient choose to perform VBL and continue VBL every 4 weeks until varices are eradicated **(Tripathi D et al., 2015).**

Table (1): Primary prophylaxis treatment for variceal bleeds **(Whitaker A, 2017)**

Variceal Classification	Treatment	EGD Screening
No Varices	none	CC: every 2-3 years
Small varices without risk factors	± non-selective β–blocker	CC: every 1-2 years, if no β-blocker DC: yearly
Small varices with risk factors	non-selective β–blocker	None
Medium/large varices without risk factors	non-selective β-blocker	None
Medium/large varices with risk factors1	non-selective β-blocker or banding	None

3-Secondary prophylaxis

The goal of secondary prophylaxis is to prevent further complications of liver cirrhosis, including further episodes of variceal haemorrhage and death. Once a patient has had one episode of variceal haemorrhage, they are at much greater risk of having a second episode (60% within the first year

with a mortality of 33%) (**Garcia-Tsao G et al., 2017**Secondary prophylaxis is by the combination of NSBBs for life and repeating VBL until variceal eradication **(De Franchis, 2015, Garcia-Tsao G et al., 2017).** NSBBs are the main stay of treatment and should be used in all patients unless there are contraindications **(De Franchis, 2015).** A recent double-blind RCT suggests that adding simvastatin may improve survival in these patients **(Abraldes et al., 2014**). Side effects of NSBB are reversible but cause discontinuation of therapy in about 15% of cases **(Garcia-Tsao G et al., 2017).**

It should be noted that carvedilol is not yet recommended in this setting as there are no randomized controlled trials in secondary prophylaxis **(de Francis, 2015**). Some studies have raised caution for the use of propranolol/nadolol in patients with end-stage liver disease **(Mandorfer M et al., 2014).** In patients with refractory ascites it is recommended that NSBBs are reduced or discontinued if systolic blood pressure decreases **(Serste T et al., 2010).**

The recent BAVENO VI consensus **(De Franchis, 2015**) proposed that in patients with refractory ascites and (i) systolic blood pressure<90 mmHg, or (ii) SCr >1.5 mg/dl, or (iii) hyponatraemia<130mmol/L, the NSBB dose should be reduced or even temporarily discontinued. Abrupt interruption of beta-blockers for a mean of three to six days was recently found not to be associated with neither an apparent increase in the risk of variceal bleeding nor a haemodynamic rebound. **(Payance A et al., 2016).** If NSBB intolerance occurs, EBL should be considered as an alternative in primary prophylaxis. In the setting of refractory ascites and secondary prophylaxis, covered TIPS placement may be considered if the patient is an appropriate candidate **(De Franchis, 2015**).

Monitoring the HVPG during the drug therapy with NSBB is called HVPG guided therapy. HVPG-guided therapy may improve the outcomes achieved with current first-line therapy combining NSBBs and EBL **(Sauerbruch T et al., 2015),** and may achieve a similar survival as TIPS, which is the most effective therapy in terms of preventing bleeding. HVPG-guided therapy can be used when available. However, this approach has relevant drawbacks such as invasiveness and limited availability and, therefore, cannot be widely recommended. **(Villanueva C et al., 2017)**

Treatment of acute variceal bleeding :

1-General measures:

The management of the patient with acute variceal bleeding (AVH) includes treating the hypovolemic shock (with volume replacement and transfusion) and preventing bleeding-associated complications (e.g. hepatic decompensation, renal failure and bacterial infections). Initial resuscitation (stabilization of airway, breathing and circulation) aims at maintaining a sufficient O_2 delivery to the tissues **(Augustin S et al., 2020).**

Blood volume should be restorted rapidly but with caution for keeping hemodynamic stability and a hemoglobin level of between 7-8 g/dL considering other factors as cardiovascular disorders, age, hemodynamic status and ongoing bleeding **(de Franchis, 2015).** This recommendation depends

on experimental studies which identified that restoration of all lost blood elevates portal pressure to levels above the normal level with more rebleeding and mortality**(Augustin et al., 2020).**

Also, vigorous resuscitation with saline have to be avoided because this may precipitate rebleeding and also worsen or precipitate the accumulation of ascites or fluid at other sites **(Castaneda B et al., 2019).** The transfusion of fresh frozen plasma and platelets can be considered in patients with significant coagulopathy and/or thrombocytopenia **(BCSH et al., 2008).**

Bacterial infection is an important indicator in the prognosis of variceal bleeding, with spontaneous bacterial peritonitis (50%) is the most frequent infection, followed by urinary tract infection (25%) and pneumonia (25%). Using prophylactic antibiotics in patients with variceal bleeding may decrease rebleeding and mortality **(Goulis J et al., 2008 and Bernard B et al., 2009).**

The risk of bacterial infection and mortality are very low in patients with Child-Pugh A cirrhosis. Individual patient risk characteristics and local antimicrobial susceptibility patterns must be considered when determining appropriate first line acute variceal haemorrhage antimicrobial prophylaxis at each centre. Intravenous ceftriaxone 1 g/24 h should be considered in patients with advanced cirrhosis, in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis **(de Franchis, 2015).**

Lactulose or rifaximin may prevent hepatic encephalopathy (HE) in patients with cirrhosis and upper GI bleeding. Episodic HE should be treated with lactulose (25 ml q 12 h until 2–3 soft bowel movements are produced, followed by dose titration to maintain 2–3 soft bowel movements per day) **(de Franchis, 2015).**

1-Specific measures:

Pharmacological Therapy

Variceal pressure is reduced by vasoactive drugs through reducing variceal blood flow. Terlipressin is the 1st choice, as it is the only drug that improves survival, while somatostatin or octreotide are the 2nd choice **(Levacher S et al., 2015 and Abraldes J et al., 2014).** Terlipressin is vasopressin analogue and is effective as endoscopic injection sclerotherapy. It acts through lowering the portal pressure by constriction of the splanchnic arterioles, so causing increase in resistance to blood inflow into the gut. The dose is 2mg/6h intravenous for 48 hours. It may be continued in a dose 1mg/4-6h for further 72 hours. As regard side effects, abdominal pain is the commonest side effect, while less than 3% of the patients may have serious side effects including peripheral or myocardial ischemia **(Levacher et al., 2015).** Hyponatremia has been described in patients under terlipressin, especially in patients with preserved liver function. Therefore, sodium levels must be monitored **(de Franchis, 2015).**

Octreotide is a synthetic analogue of somatostatin with longer half-life. It acts like somatostatin by reducing the portal pressure via increasing splanchnic arterial resistance. It also inhibits glucagon, a vasodilator peptide. Its safety is close to that of somatostatin. Treatment is kept up to 5 days to prevent early rebleeding **(Escorsell A et al., 2011 and Abralde J et al., 2014).** Usage of octreotide with sclerotherapy significantly reduces early rebleeding which may be due to its sustained ability

to prevent postprandial elevation of portal pressure **(CorleyD et al., 2020 and Abraldes J et al., 2014)**. Octreotide is superior to vasopressin and comparable to terlipressin **(D'Amico G et al., 2019)**.

Despite the beneficial effect on control of bleeding, somatostatin didn't decrease mortality. Side effects with somatostatin include vomiting, nausea, and hyperglycemia which occur in up to 30% of patients. However, serious side effects with somatostatin are rare **(D'Amico G et al., 2019)**.

Endoscopic Treatment

Inspite that both injection sclerotherapy and variceal band ligation are effective in controlling the acute variceal bleeding, band ligation is better for the initial control of bleeding and is accompanied with less side effects and improved mortality **(Cordon J et al.,2021)**. Thus, band ligation is the treatment of choice while injection sclerotherapy replaced it if not available or if technically difficult **(Villanueva C et al., 2017)**.

Table (2): Comparison of EGD therapies for variceal treatment **(Whitaker, 2017)**

EGD therapy	Sclerotherapy	Banding
Technique	Injection of sclerosant causing thrombosis in vessel and inflammation in surrounding tissue	EGD places rubber bands around bleeding varices
Duration	5 sessions every 14 days until eradicated	4 sessions every 14 days until eradicated
Benefits	Cheap Easy to perform	Fewer complications
Complications	• Esophageal ulcers • Bleeding ulcers • Fever • Retrosternal chest pain • Dysphagia • Esophageal strictures • Bacteremia and infections • ↑ portal pressure	• Shallow ulcers • Bleeding ulcer • Transient dysphagia, chest discomfort • Esophageal laceration and perforation • Retrosternal chest pain • Esophageal strictures

In 10 to 20% of patients, variceal bleeding is unresponsive to initial endoscopic and/or pharmacologic treatment. If bleeding is mild and the patient is stable, a second endoscopic therapy (if technically possible) might be attempted. In about 60-90% of massive variceal bleeding, hemostasis is achieved through balloon tamponade (balloon inflation of Sengstaken-Blakemore tube). Because of its severe adverse events, it should only be used for a short duration (< 24 hours) as a bridge until definitive treatment is established **(D'Amico G et al., 2019)**.

Self-expanding covered oesophageal metal stents may be as efficacious and a safer option than balloon tamponade in refractory oesophageal variceal bleeding. Persistent bleeding despite

combined pharmacological and endoscopic therapy is best managed by PTFE covered TIPS **(de Franchis, 2015).**

Prevention of complications

Prevention of complications should run simultaneously to haemostatic therapies from admission of patients with cirrhosis and acute GI bleeding. The main complications, whatever the cause of bleeding, include bacterial infections (such as aspiration pneumonia or spontaneous bacterial peritonitis(SBP)), hepatic encephalopathy and deterioration of renal function. Bacterial infections are observed in more than50% of patients and may already be present at the time of bleeding (20%) acting as a precipitating event **(Villanueva C and Escorsell A, 2014).** Moreover, the presence of bacterial infection is an independent predictor of failure to control bleeding and death. Antibiotic prophylaxis is recommended because it reduces the incidence of infections and improves control of bleeding and survival **(Garcia-Tsao G et al., 2017).** Ceftriaxone (1g/24 h) for up to seven days, is the first choice in patients with advanced cirrhosis, in those on quinolone prophylaxis and in hospital settings with high prevalence of quinolone resistant bacterial infections **(Tandon et al., 2015).** Oral quinolones (norfloxacin 400 mg b.i.d) can be used in the remaining patients. Renal function should be preserved by the adequate replacement of fluids and electrolytes. Nephrotoxic drugs (such as aminoglycosides and nonsteroidal anti-inflammatory drugs (NSAIDs) as well as beta-blockers, vasodilators and other hypotensive drugs should be avoided during the course of AVH. Oral non-absorbable disaccharides may be used to prevent the development of hepatic encephalopathy **(De Franchis, 2015).**

Proton pump inhibitors (PPIs) have not shown efficacy for the management of AVH. However, a short course therapy with PPI after EBL may reduce the size of post-banding ulcers **(Shaheen et al., 2005).** Balloon tamponade should be used in case of massive bleeding, as a temporary "bridge" until definitive treatment can be instituted and for a maximum of 24 h, preferably under intensive care facilities **(De Franchis, 2015).** Because of the high risk of aspiration pneumonia, tamponade should be preceded by prophylactic orotracheal intubation in comatose patients. Removable covered and self-expanding oesophageal stents are an alternative to balloon tamponade, and may have lower rates of serious adverse events **(Escorsell A and Pavel O., 2016).**

Despite therapy with vasoactive drugs plus EBL and prophylactic antibiotics, up to 10–15% of patients with AVH have persistent bleeding or early rebleeding.If none of the above measures has managed to control an acute variceal haemorrhage, then the next step in the treatment algorithm is TIPSS; this may necessitate the urgent transfer of the patient to a specialist liver unit, as the appropriate interventional radiology expertise may not exist in every centre. Studies have shown that salvage TIPSS managed to achieve control of bleeding in 90–100% of cases, with re-bleeding rates of 6–16%.Mortality was 75% in hospital and 15% at 30 days **(Vangeli M et al., 2020).** When TIPS is not feasible or in case of modest rebleeding, a second endoscopic therapy may be attempted while vasoactive drugs can also be optimized, by doubling the dose of somatostatin and/or changing to terlipressin if not used previously **(Garcia-Tsao G et al., 2017).**

Early TIPSS (before onset of treatment failure) within 72 hours of admission is associated with significantly lower mortality and treatmen failure **(Garcia-Pagan et al., 2010).** High-risk patients

have been defined as those with a HVPG of >20mmHg, Child-Pugh class C with a score of 10–13,Child-Pugh B with active bleeding seen endoscopically despite treatment with intravenous vasopressors **(Garcia-Pagan et al., 2010).** Despite early TIPSS in these high-risk patients, observational studies have failed to demonstrate long-term survival benefit **(Rudler M et al., 2014).**

Surgery

Shunt surgery reserved mainly for Child-Pugh A patients who has been shown to be an effective option as salvage treatment for patients where there is failure to control bleeding with VBL and vasopressors **(Sanyal AJ et al., 2006).** Portocaval shunt surgery is not routinely used in most centres, especially since the increased use of minimally invasive and simpler interventional radiology techniques such as TIPSS .Liver transplantation is always an option but rarely used or appropriate in the setting of acute variceal haemorrhage. It is mainly considered for patients who bleed while on a transplant waiting list. To date, there are no studies comparing VBL vs TIPSS vs. liver transplantation and there are no trials on the use of liver transplantation in the context of active variceal bleeding. If the patient survives an acute episode, then of course they can be referred for elective assessment for liver transplantation assuming

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