Chapter

Endoscopy in Management of Portal Hypertension

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Abstract

Portal hypertension (PH) is a serious consequence of several disease states affecting prehepatic, intrahepatic, or posthepatic portal circulation. Backpressure caused by PH transmits through the collaterals to form varices at various sites. PH also leads to hyperdynamic congestion and altered gastrointestinal mucosal immune response, resulting in portal hypertensive gastropathy (PHG), portal hypertensive enteropathy (PHE), and portal colopathy (PC). These PH associated phenomena may lead to torrential life-threatening bleed or chronic blood loss leading to debilitating chronic anemia. Endoscopy plays a pivotal role in the management of these patients both for diagnostic and therapeutic purpose. The choice of therapeutic strategy depends on many factors: severity of the disease, patient's clinical performance, and whether it is done as an emergency or as a prophylactic approach. In this chapter, we evaluate the endoscopic management of patients with the gastrointestinal complications of PH.

Keywords: portal hypertension, esophageal varices, gastric varices, portal hypertensive gastropathy, gastric antral vascular ectasia, portal hypertensive enteropathy, portal colopathy

1. Introduction

Portal hypertension (PH) is a serious consequence of disease states affecting prehepatic, intrahepatic, or posthepatic portal circulation. Liver cirrhosis, which leads to sinusoidal hypertension, is the most frequent etiology of PH. Cirrhosis causes structural distortion in the liver architecture accompanied by the rise in local intrahepatic vasoconstrictors. Cirrhosis also causes an increase in systemic vasodilation and increased cardiac output leading to increased portal blood flow. When portal pressure, measured as hepatic vein portal gradient (HPVG), is >10 mm of Hg, it leads to development of portosystemic collaterals (**Figure 1**). These collaterals arise due to recanalization of fetal vascular channels, reversal of flow within adult veins, and/or because of neoangiogenesis [1]. Backpressure caused by PH transmits through these collaterals to perforating veins and the submucosal vessels they supply, whereby varices may form.

A PH related increase in the portal vein pressure leads to hyperdynamic congestion in the gastric, small intestinal, and colonic mucosa. The mucosa undergoes microcirculatory changes, such as submucosal angiogenesis and vascular ectasia, that impair its integrity and promote its susceptibility to damage. Moreover, local

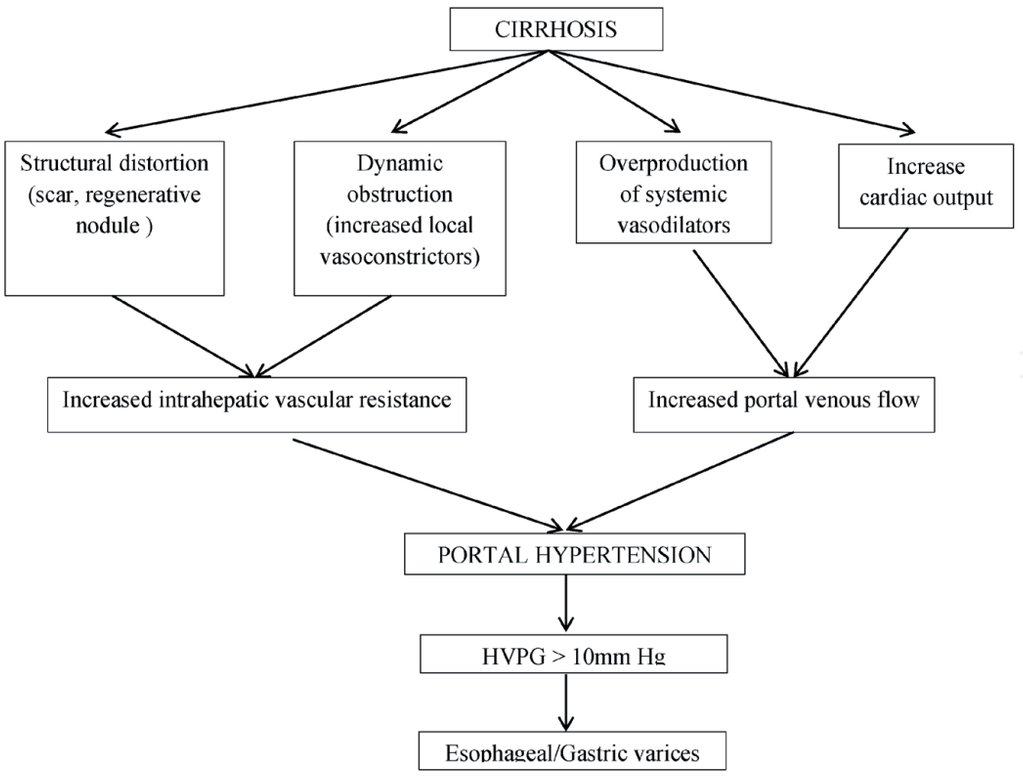


Figure 1.
Pathophysiology of formation of varices in cirrhosis.

immune mucosal defense mechanisms are impaired in PH. All these lead to portal hypertensive gastropathy (PHG), portal hypertensive enteropathy (PHE), and portal colopathy (PC) [2, 3]. This chapter focuses on the endoscopic management of varices, PHG, Gastric antral vascular ectasia (GAVE), PHE, and PC.

2. Esophageal varices

Esophageal varices are present in 30–40% of patients with Child A cirrhosis and approximately 85% of those with Child B/C cirrhosis [4]. Despite improved surveillance and treatment, the rate of variceal hemorrhage (VH) continues to be 10–15% per year, with an 6-week mortality of 15–25% [5]. Mortality risk is particularly high when VH is associated with acute kidney injury (AKI) and/or concomitant bacterial infections [6]. Recurrent VH occurs in 60% of patients without treatment [7].

Considering the high-risk of death when VH occurs, implementing surveillance strategies to prevent bleeding and death should be pursued actively in patients with cirrhosis. Once the patient is diagnosed with cirrhosis, a periodic surveillance endoscopy is warranted to look for esophageal varices. Other modalities such as video capsule endoscopy (VCE), computed tomography (CT) scan, or Fibroscan have been assessed for their role in detecting esophageal varices [8, 9]. However, endoscopy is still regarded as the investigation of choice.

2.1 Primary prophylaxis

The risk factors of VH are the large size of varices, red signs, and the severity of liver disease [10]. Primary prophylaxis must be initiated in "high-risk varices" **(Figure 2a)**. This includes small varices (<5 mm) with red color signs, any varix in Child-C patients or large varices (>5 mm) irrespective of Child-Pugh

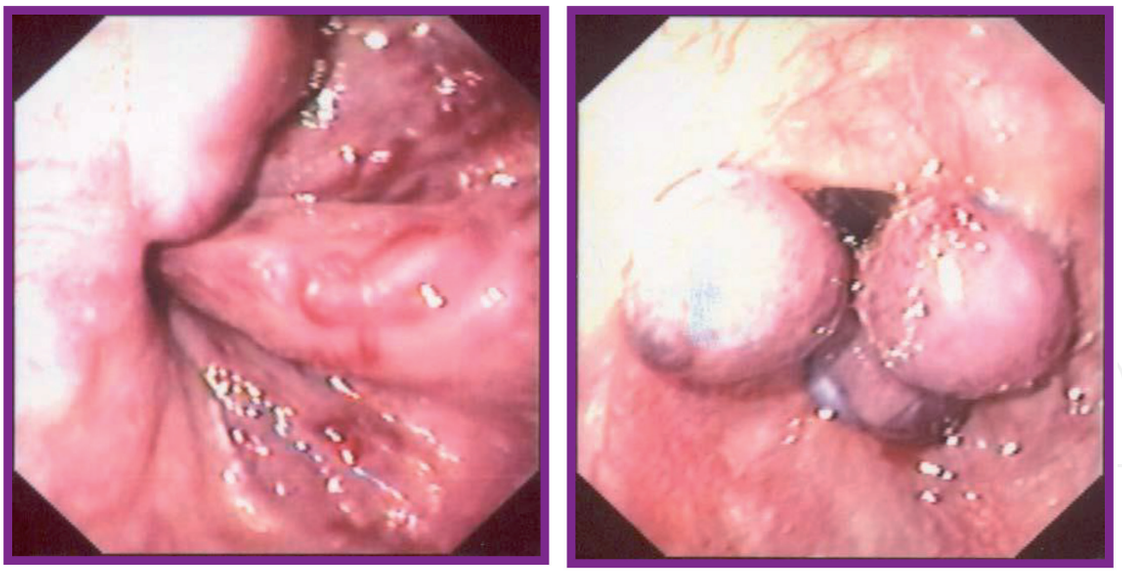


Figure 2.
Endoscopic appearance of esophageal varix. (a) Large esophageal varix with red color signs, (b) esophageal varix after endoscopic band ligation.

classification [11]. In patients with "low-risk varices" or no varices, surveillance endoscopy should be undertaken at interval of 2–3 years, depending on the severity of the liver disease and whether the liver injury is ongoing or not (**Figure 3**). The patients with active alcoholism, non-alcoholic steatohepatitis (NASH), hepatitis B and C with detectable viral load are some examples of ongoing liver injury.

The primary prophylaxis of "high-risk varices" involves pharmacological prophylaxis using a nonselective beta-adrenergic blockers (NSBB) or endoscopic band ligation (EVL). NSBBs such as propranolol and nadolol reduce cardiac output and splanchnic blood flow through nonselective beta-blockade, and the unopposed effect of alpha-1 adrenergic receptors leads to splanchnic vasoconstriction. This reduces the portal pressure and its consequential complications. Carvedilol, an NSBB with

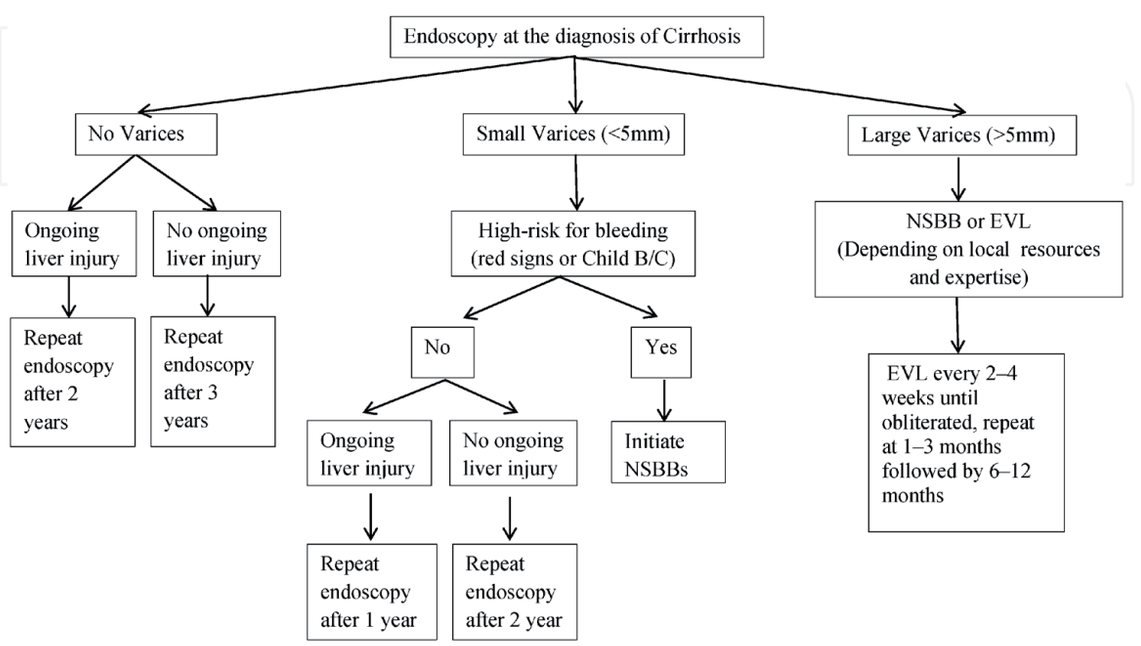


Figure 3.
Algorithm for surveillance and primary prophylaxis of esophageal varix.

intrinsic anti-alpha-1 receptor activity, reduces both porto-collateral and intrahepatic resistance. However, this is at the cost of more profound effects on the systemic arterial pressure, particularly in decompensated patients. Carvedilol is therefore, preferred in patients where NSSB are contraindicated or produce side effect.

EVL (**Figure 2b**) involves the placement of rubber rings on variceal columns, which are sucked into a plastic hollow cylinder attached to the endoscope tip. Ligation causes occlusion of the varix and subsequent thrombosis with ischemic necrosis of the mucosa. Band placement should be limited to the distal 8 cm segment of the esophagus in order to target the palisade drainage and perforating zones. Bands should be placed helically, moving distal to proximal to allow the maximum number of bands to be applied while avoiding overlapping circumferential placement. More proximal placement has less efficacy and may cause post ligation retrosternal discomfort. Complications after EBL occur in approximately 2–20% of the patients and include transient dysphagia, retrosternal pain, esophageal stricture, ulceration, perforation, and infection [12]. Occasionally, massive bleeding can occur, either from recurrent variceal rupture or from post-ligation ulceration.

It is generally recommended that small varices with red signs should be treated with NSBBs. Large varices can be treated with either NSBBs or EBL. The treatment choice is based on local resource and expertise, patient preference, contraindications, and adverse events [11, 13, 14].

2.2 Acute esophageal variceal hemorrhage (AVH)

Ruptured esophageal varices contributes to 70% of all the upper gastrointestinal (GI) bleeding episodes in patients with portal hypertension [15]. Initial treatment should always target restoring the euvolemic status. Restrictive blood transfusion strategy is adequate in most patients with GI bleed [16]. Vasoactive drug therapy and antibiotic prophylaxis should be initiated as soon as AVH is suspected [11]. After adequate resuscitation, an endoscopic evaluation should be carried out in patients with acute variceal bleed, in the first 12 hours after admission [13]. **Table 1** shows various modalities which can be used to treat esophageal variceal bleed.

2.3 Endoscopic variceal band ligation (EVL)

EVL is the preferred endoscopic therapy for active bleeding, as it allows greater bleeding control, with lower adverse events, and improves survival compared to endoscopic sclerotherapy (ES) which was practiced earlier [17]. In AVH, EVL should be preferentially targeted toward the culprit variceal column evidenced by the ongoing ooze or presence of stigmata of hemorrhage. However, during active

Endoscopic Therapy
• Variceal band ligation (EVL)
• Sclero therapy/ Glue injection
• Tamponade using
○ SB tube
○ Metal stents
• Argon plasma coagulation
TIPS

Table 1.
Therapeutic options for control of acute esophageal variceal bleed.

bleeding, banding at the gastroesophageal junction may reduce bleeding, allowing visualization and appropriate targeting of subsequent bands.

Despite adequate therapy with vasoactive drugs combined with EVL, up to 10–15% of patients with variceal hemorrhage have persistent bleeding or early rebleeding [18]. Transjugular intrahepatic portosystemic shunts (TIPS) should be considered as a rescue therapy of choice in this group of patients [13]. When TIPS is not feasible or in case of modest rebleeding, a second endoscopic therapy with repeat EVL or alternate methods may be attempted, and vasoactive drugs doses should also be optimized.

2.4 Endoscopic sclerotherapy and glue injection

The sclerosant injection acts by precipitating inflammation and thrombosis of the varix. ES involves intravariceal injection of sclerosant at and just distal to the site of the bleeding, or perivariceal injection performed adjacent to a varix. Injection should be first performed at the bleeding site, followed by perivariceal or intravariceal injection starting from the GE junction, with proximal injections at 2-cm intervals, extending up to 5 cm to 6 cm from the GE junction. Sclerosants used include sodium tetradecyl sulfate (Food and Drug Administration approved), sodium morrhuate, ethanolamine oleate, polidocanol, or absolute alcohol.

A meta-analysis of 14 studies found that EVL is better than ES in terms of lower rates of rebleeding and complications and a higher rate of variceal eradication [19]. The complications related to ES occur in up to 40% of patients, and include esophageal ulceration, stricture, perforation, pleural effusion, hemothorax, pulmonary thromboembolism, pericarditis, mediastinitis, pneumothorax, renal dysfunction, and even death [20]. Though EVL is the therapy of choice for the management of bleeding varices, there are a few indications where EVL is technically demanding, and ES can be utilized. This includes massive ongoing bleed when visualization is impaired, when adequate tissue suctioning into the cap is not possible due to scar, and in young children.

Glue injection have also been performed for active variceal bleeding. Overall, there is no definitive evidence supporting the use of cyanoacrylate injection for the management of bleeding varices or for VH prophylaxis. Tissue adhesive injection may be considered in conjunction with sclerotherapy. However, a RCT did show that using n-butyl cyanoacrylate and sclerosant injection in conjunction, resulted in lower rebleeding and mortality compared to using sclerotherapy alone [21].

2.5 Tamponade using balloons or metal stents

For persistent VH, where EVL has failed, as well as for EVL-related ulcer bleeding, balloon tamponade (BT) using Sengstaken-Blakemore (SB) tube and emergency TIPS have been advocated [13]. SB tube is associated with many complications and rebound bleeding. Performing TIPS in emergencies may not be feasible in many centres. Besides, there are cost issues and a definite risk of encephalopathy in the presence of advanced liver dysfunction [22]. Covered self-expanding metal stents (SEMS) with distinctive designs are used to produce an effective tamponade, controlling persistent variceal bleeding and ulcer bleeding following VBL [23, 24].

Initially, the Choo stent (diameter 18 mm, length 140 mm, NES – 18 – 080 – 070, MI Tech Co., Ltd) and the EllaBoubella-Danis stent (diameter 20 mm, length 95 mm, Ella-CS, Hradec Kralove, Czech Republic) were used. Despite demonstrating efficacy, these stent designs were not ideal for deployment and use in variceal bleeding; hence the SX-ELLA Danis Stent (Ella-CS, Hradec Kralove, Czech Republic) was designed [23]. SX_ELLA Danis Stent (**Figure 4**) is the most commonly used

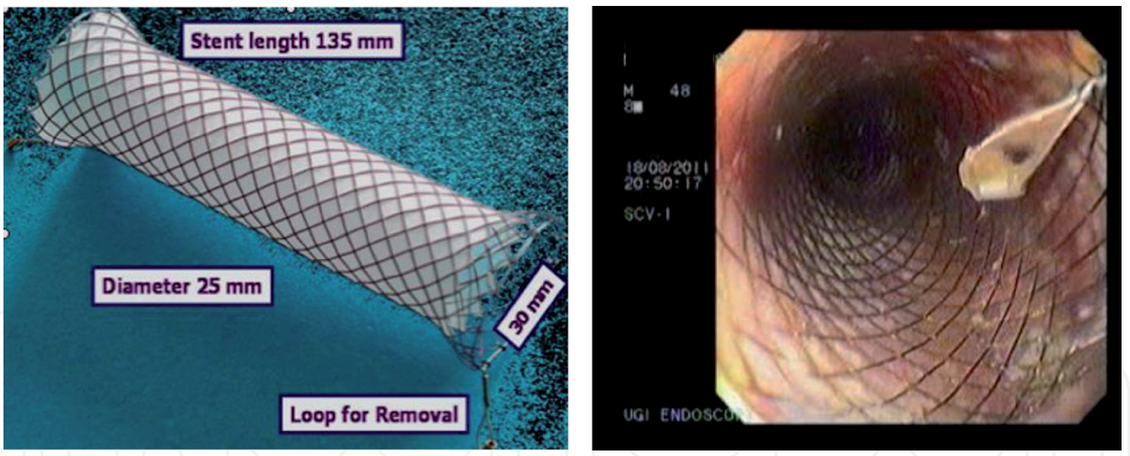


Figure 4.
Ela stent: SX ELLA STENT. A) Stent design, B) stent in esophagus.

stent for the treatment of persistent VH. It differs from the Choo stent and the EllaBoubela-Danis stent in having a balloon-style delivery system. These stents are made of nitinol, measuring 13.5 cm in length with a diameter of 25 mm in the shaft and 30 mm at the ends. The stents are placed usually over an endoscopically placed guidewire but can also be inserted at bedside without the need of an endoscope. The stent's unique delivery system uses a gastric positioning balloon placed just distal to caudal end of the stent. The correct positioning of the stent in the distal half of the esophagus is established by inflating the gastric balloon and retracting the catheter assembly until the gastric balloon hits against the cardia. The stent is then released, and the gastric balloon is deflated, and the assembly catheter is removed [24]. These stents act by causing a steady mechanical compression causing an immediate tamponade at the variceal bleed site. Compared to SB tube, these stents allow oral feeding and endoscopic assessment of rebleed.

In a meta-analysis of 12 studies, which evaluated SEMS placement for refractory esophageal variceal hemorrhage, the reported clinical success (absence of bleeding within 24 hours of SEMS placement) rate was 96% (95% CI, 0.90–1.00) and technical success (guidewire-assisted endoscopic SEMS deployment) rate was 97% (95% CI, 0.91–1.00). Adverse events associated with the placement of SEMS include stent migration (28%), rebleeding (16%), and ulcer. However, there was no significant difference in mortality compared to balloon tamponade [25]. Removal of SX-ELLA Danis stent is advised within 2 weeks following stent insertion, under endoscopic guidance using the custom PEXElla extractor (Ella-CS) or usual foreign body forceps [26].

2.6 Argon plasma coagulation (APC)

APC is an electrosurgery-based, non-contact, multi-directional coagulation method. A high-frequency current is applied to the target tissue through an argon plasma jet with a constant depth of energy penetration (maximum 4 mm). APC has been used to coagulate the distal esophageal mucosa after eradicating esophageal varices by endoscopic variceal ligation to reduce the rate of variceal recurrence and need for rebanding. This technique is generally recommended as secondary prophylaxis for esophageal variceal bleeding in those who have contraindications, are intolerant, or are non-compliant to NSSB [27]. A meta-analysis of four randomized controlled trials (RCT) compared the safety and efficacy of EVL alone, with EVL along with APC, for secondary prophylaxis of esophageal variceal bleeding. Across the 4 RCTs, combination therapy showed significantly lower variceal recurrence

rates (relative risk 0.19). There was no difference in re-bleeding or mortality. Fever occurred more often after combination therapy [28].

After ensuring the complete eradication of varices, APC is initiated 2 to 3 weeks after the last EVL session. APC is generally performed at a gas flow rate of 1.2–2 L/min. The power setting of the APC current generator is adjusted at 50 to 70 W. The entire esophageal mucosa proximal to the esophageal junction is coagulated with APC in 2 sessions at 2-week intervals. In each session, one half of the mucosa is ablated thermally starting at the esophagogastric junction by retracting the probe proximally, while delivering thermal energy creating longitudinal parallel stripes of coagulated tissue.

3. Gastric varices

Gastric varices (GV) are the source of bleeding in 5–10% of patients with PH, second only to the esophageal variceal bleed [15]. GV is, however, relatively more common in non-cirrhotic portal hypertension (NCPH) and extrahepatic portal vein obstruction (EHPVO) occurring in 1/4th and 1/3rd of patients, respectively [20].

The GV classification system aligns with the therapeutic distinction and categorizes GV based on whether they are contiguous with esophageal varices or not, and as per their location in the stomach (**Figure 5**) [29]. Gastroesophageal varices (GOV) are contiguous with the esophageal varices extending either into the lesser curvature (GOV1) or the fundus along the greater curvature (GOV2). These varices share the pathophysiology of esophageal varices, arising from the left gastric vein and originate in the lamina propria. Isolated Gastric Varices (IGV) are distinct from GOV and can be located either in the cardia (IGV1) or outside of the cardia and fundus, usually the antrum or pylorus (IGV2). These arise from the short and posterior gastric veins and originate in the submucosa.

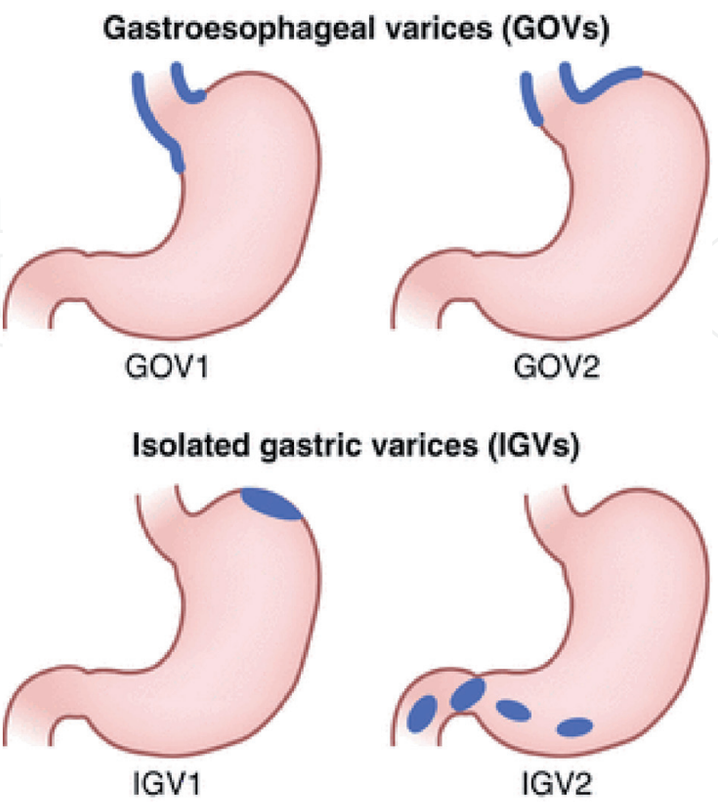


Figure 5.
Sarin Classifiaction of gastric varix. GOV- gastroesophageal varix, IGV- isolated gastric varix.

Gastric variceal bleeding (**Figure 6**), although less common, has the predisposition to be more severe, associated with higher blood transfusion requirement, and increased morbidity, and mortality compared with esophageal variceal bleeding [30]. The probable cause for this is a large submucosal component of GV, the vascular structures feeding and draining the gastric varix, and, also, the lack of widespread expertise. Bleeding risk is significantly higher for the IGV1 (77%) and GOV2 (55%), than for GOV1 or ectopic varices (10%) [29]. EHPVO more commonly results in IGV1 varices, whereas cirrhosis related portal hypertension more commonly results in GOV2 varices.

3.1 Primary prophylaxis

There is limited data on the primary prophylaxis of GV bleeding. In a RCT with a sample size of 89 patients, endoscopic glue was found to be more effective than the beta-blocker therapy in preventing the first GV bleeding, the risk of not having bleed, being 87% vs. 62% respectively. There was a survival advantage also in the patients with GOV2 and IGV1. High-risk factors for first bleeding from GVs are variceal size >20 mm, MELD score > 16, and the presence of severe portal hypertensive gastropathy (PHG) [31] and these may be suitable for glue injection. The algorithm for the management of gastric varix, including role of primary prophylaxis is depicted in **Figure 7**.

3.2 Acute gastric variceal hemorrhage (AGVH)

Medical management of suspected gastric variceal bleeding includes airway protection, restrictive blood transfusion, vasoactive agents, antibiotics, and admission to the intensive care unit. **Table 2** shows various modalities which can be used to treat GV. Endoscopic therapy is the initial treatment of choice. The methods utilized often depend on the local availability and experience. An algorithm for management of GV is shown in **Figure 7**.

3.3 Glue injection

N-butyl-2-cyanoacrylate, is a monomer that rapidly undergoes exothermic polymerization upon contact with living tissues, getting transformed from liquid to a hard, brittle acrylic plastic. This tissue adhesive is used to treat bleeding GV.

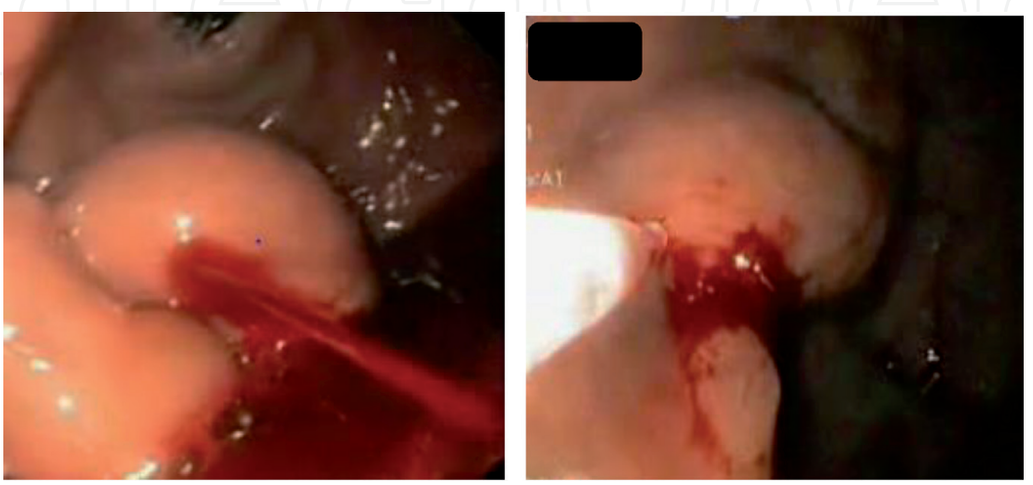


Figure 6.
Endoscopic appearance of gastric varix. (a) Spurting bleeding from the gastric varix, (b) hemostasis after glue injection.

Endoscopic therapy
Glue
Coil
Thrombin
Sclerotherapy
Interventional Radiology
TIPS
BRTO/BATO
Surgery

Table 2.
Therapeutic options for control of acute gastric variceal bleed.

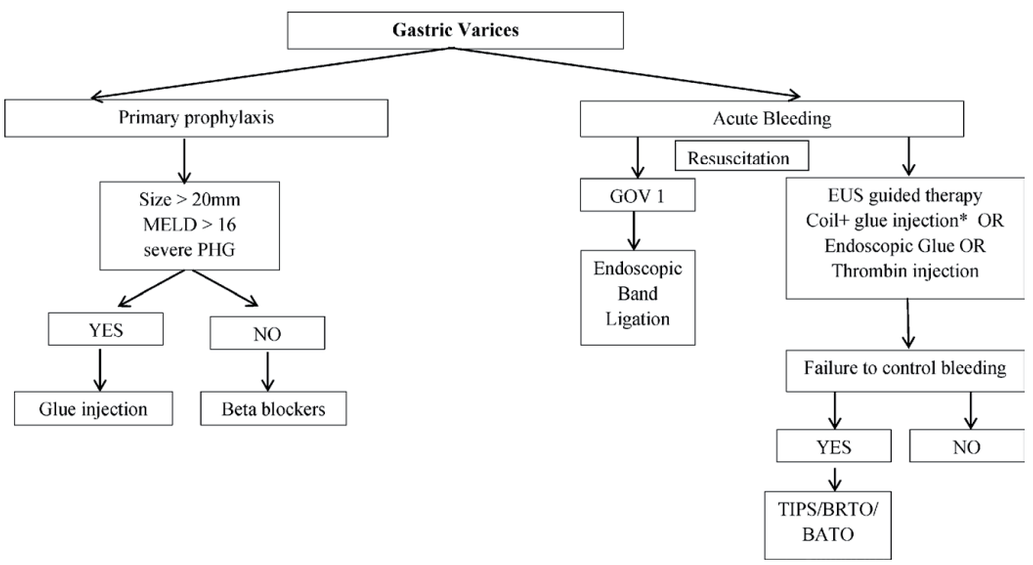


Figure 7.
Algorithm for management of gastric varix. Depending the expertise available. TIPS Transjugular intrahepatic portosystemic shunt. BRTO balloon-occluded retrograde transvenous obliteration. BATO balloon-occluded Antegrade Transvenous obliteration.

For the glue injection, a therapeutic endoscope with a 3.7 mm working channel may be preferred for the accurate control of the injector catheter. The injection catheter should be primed with distilled water (DW) or normal saline (NS) (0.8–1 ml) to fill up the dead space. The gastroscope is placed in a retroflexed position close to the target varix. The suction is turned off, and the injection catheter with the needle still withdrawn, is advanced without variceal contact juxtaposed to the target varix. The needle is then pushed out directly into the varix, and glue is injected in 1 ml aliquots by using NS or DW solution to flush the glue into the varix. The needle should be immediately withdrawn after the glue injection to prevent entrapment into the varix. While withdrawing the needle, the flushing of a steady stream of the solution is aimed at the varix's puncture site. The varix's blunt palpation is done by catheter or biopsy forceps, and additional glue is injected until the varix is 'hard' to palpate.

Overall success in term of hemostasis is noted in 84–100% of GV treated with glue. Technical complications related to glue injection include needle entrapment in a varix, exposure to the eyes of endoscopists or the assistants, or endoscope damage. Clinical complications from cyanoacrylate injection occur in up to 7% of cases and involve systemic embolization, sepsis, gastric ulcer, rebleeding due to cast extrusion, and mesenteric hematoma. Embolisation can be fatal and can involve

lung, portal vein, coronary arteries, spleen, or even brain with risk increasing more with excessive and forceful glue injection. Visceral fistulization from the stomach into the pleura or mediastinum also may occur after unintentional paravariceal glue injection [32].

3.4 Sclerosant injection

Injection of sclerosants like tetradecyl sulphate and alcohol is one of the oldest techniques endoscopists used, in order to control acute gastric variceal bleeding. Sclerotherapy involves injection of a combination of para- and intra-variceal injections, or 5–10 ml of intravariceal sclerosant injection into the actively bleeding GV. Rebleeding rate is reported to be between 10 and 20%.

On comparing glue injection versus sclerotherapy in a RCT of 37 patients with IGV-1, glue was more efficacious than alcohol sclerotherapy in immediate hemostasis (89% vs. 62%), variceal obliteration (100% vs. 44%), and achieving quicker variceal obliteration (2 weeks vs. 4.7 weeks) [33]. Sclerosant injection is associated with high rates of complications, including gastric ulceration, perforation, and rebleeding (37–53%), and hence, it is not a good option in the management of GV [34, 35].

3.5 Thrombin injection

Thrombin tissue adhesives include thrombin, a human or bovine protein that affects hemostasis by converting fibrinogen to a fibrin clot. Thrombin also achieves hemostasis by altering the platelet aggregation. Human thrombin injection generally consists of 5 ml of reconstituted solution in calcium-chloride containing thrombin 500 IU/ml (Floseal; Baxter Healthcare Corporation, CA, Hayward, USA). During each session, usually 5 mL of thrombin solution is injected in a varix.

In an only RCT available which compares thrombin to cyanoacrylate injection in the control of AGVH, thrombin injection and glue injection had similar success rate (90% vs. 90.9%). However, a higher incidence of complications (51% vs. 12%) and ulcers (37% vs. 0%) were noted with glue injection as compared to thrombin [36]. Results of this study cannot be generalized as the sample size used in this study was small.

3.6 Endoscopic ultrasound (EUS) -guided therapies

EUS can improve the endoscopic management of gastric varices in many regards. These include – a) Increased detection rate of gastric varices overlooked as gastric folds. b) Ability to use doppler to confirm variceal obliteration and predicting the rebleeding risk. c) Adequate visualization of culprit gastric varix even in presence of torrential hemorrhage or blood clots and d) EUS-guided glue injection can be done precisely into a perforating vessel with preceding contrast injection to identify the feeding vessel as efferent or afferent, and thereby reducing embolization risk by enabling the use of a smaller volume of glue. e) EUS provides additional information regarding portal vein and splenic vein patency, helping to assess need and feasibility candidacy for TIPS/Balloon-occluded retrograde transvenous obliteration (BRTO) in failed cases [37].

The technique of EUS guided glue therapy involves filling the gastric fundus with water to improve acoustic coupling and visualization. The EUS is then positioned either in the distal esophagus (transesophageal-transcrural approach) or in the cardia/fundus (transgastric approach) to visualize the intramural varices and feeder vessels. EUS-directed intravascular puncture of the GV is performed using a standard FNA needle.

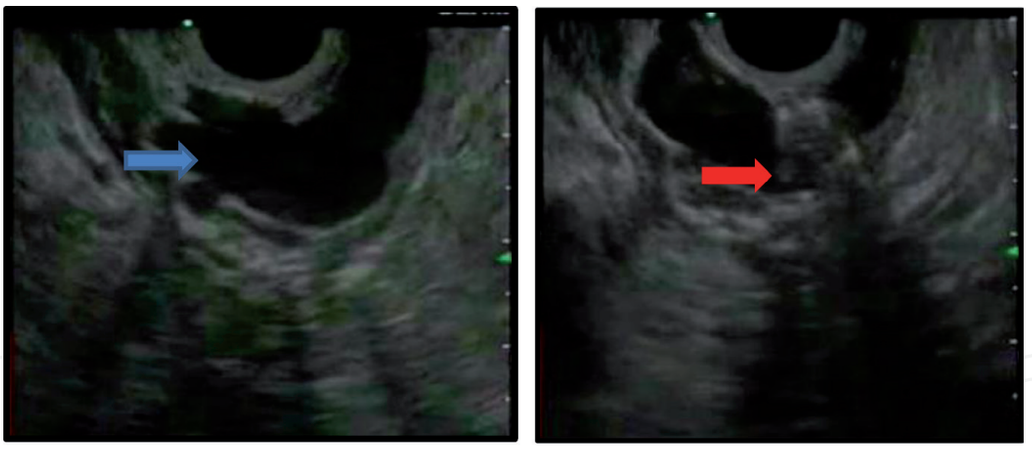


Figure 8.
Endosonographic coil embolization of the gastric varix. (a) Endosonography view of gastric varix (blue arrow) (b) Endosonography view of gastric varix after coil embolization (blue arrow).

Reports have suggested that the initial deployment of intravascular coils in the GV provides a scaffold for glue polymerization and fixation, reducing the glue requirement and inadvertent glue embolization [38] (**Figure 8**). Various commercially available coils include 0.035-inch MReye coils (extended embolus length 5 to 10 cm, coiled embolus diameter 10 mm; IMWCE 35, Cook Medical) or Hilal micro coils (extended embolus length 2 cm, coiled embolus diameter 2 mm; Embolization micro coil, MWCE, William Cook Europe, Bjeeverskov, DK). Generally, a 5-cm MReye coil are used if the vessel diameter is less than 10 mm, and a 10-cm MReye coil is used if the vessel diameter was more than 10 mm. Once the needle is inside the gastric varix, stylet is withdrawn, and the coil is deployed by advancing the stiffer part of a 0.035-inch guidewire. After coil is deployed, 1 ml aliquots of glue is injected, followed by NS flush, using the same needle. Color Doppler after treatment can confirm the absence of flow in the treated varix.

EUS-guided coil and cyanoacrylate injection was found to yield a 100% hemostatic success rate in a single-center pilot study [39]. Additionally, there were no procedure-related complications reported [39]. A recently published meta-analysis that compared treatment efficacy of EUS guided glue and coil injection with the endoscopic glue injection alone reported a statistically significant benefit of variceal obliteration in the EUS group (86.2% vs. 62.6%). The results were however, comparable in both the groups in terms of treatment efficacy, recurrence of gastric varix, early and late rebleeding [40].

3.7 Hemospray

TC-325 (Hemospray, Cook Medical, Winstom-Salem, North Carolina, United States) is a hemostatic powder which, when in contact with blood or tissue in the GI tract, becomes cohesive and adhesive, and forms a physical barrier, coating the bleeding site. Its effect lasts approximately 24 hours because the hemostatic layer sloughs off. Currently, it is only licensed for the treatment of non-variceal upper GI bleed. However, two recent studies demonstrated that Hemospray could be used as a bridge to a definitive treatment in active variceal bleeding [41, 42].

4. Ectopic varices

Ectopic varices (EcV) have a very complex anatomy. Understanding anastomosis with the splanchnic venous system is essential in managing EcV. These are rare

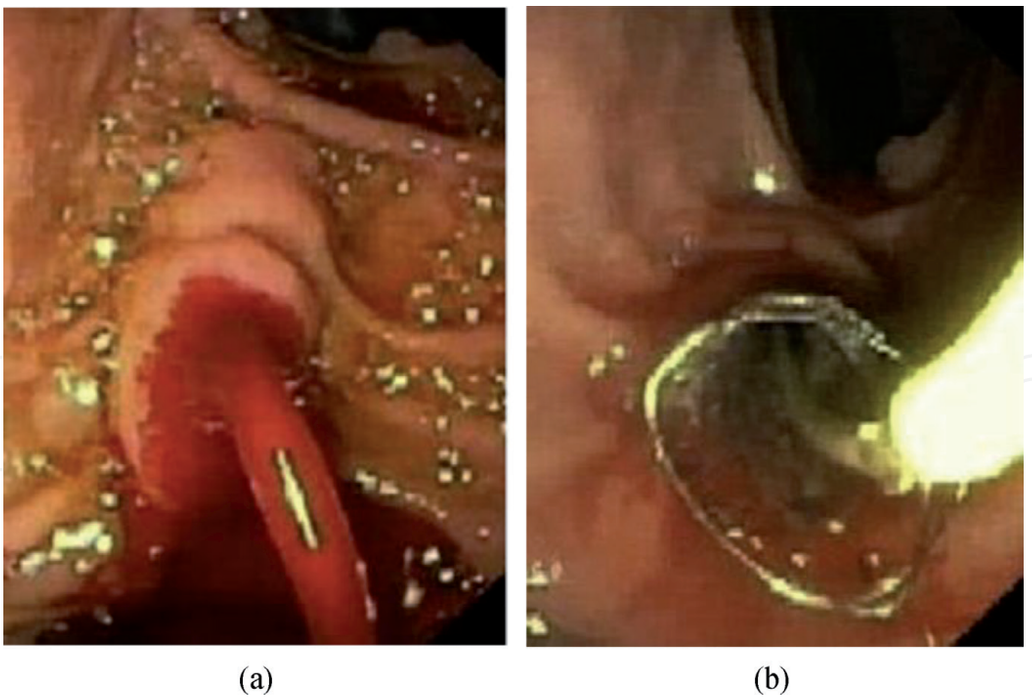


Figure 9.
Hemobilia due to choledochal varix and its treatment with metal stent. (a) Endoscopic appearance at side viewing examination showing spurting from papilla due to choledochal varix, (b) after deployment of covered self-expanding metal stent.

cause of bleeding in patients with cirrhosis and PH, accounting for only 2–5% cases [43]. They are more common in patients with prehepatic PH, occurring in 27–40% of patients with splanchnic vein thrombosis [44]. However, EcV bleed is more severe than esophageal variceal bleeding, with mortality rates up to 37.5% [45]. Ectopic varix can develop in the duodenum, small bowel, rectum, colon, gallbladder, and biliary tract, periumbilical, peristomal, and the retroperitoneal areas. Endoscopy is used for both diagnosis and therapy. Most of the EcV are within reach of standard EGD and colonoscopy. A bleeding small intestinal varix may occasionally require the use of capsule endoscopy and device-assisted enteroscopy.

The treatment of bleeding of EcV is extrapolated from the esophageal and gastric varices literature. Successful outcomes depend on local expertise, location of varices, and the technical feasibility. ES and glue injection are commonly used modalities. EVL can be used to manage the rectal and duodenal varix. Caution however, must be exercised if the varix size is bigger, as the chances of hemostasis are less and the risk of rebleeding is high. Use of APC with EBL may be considered for the prevention of variceal occurrence, as has been reported in the treatment of ileocolonic anastomotic varices [45]. Hemostatic clip placement has been reported for ectopic variceal therapy [46]. Hemobilia, due to choledochal varices, can be life-threatening. Placement of a covered biliary metal stent (**Figure 9a**, **b**) is a promising approach to achieve immediate hemostasis for bleeding from portal biliopathy and associated choledochal varix. Biliary stenting serves as salvage therapy and a bridge to elective devascularization and shunt surgery [47].

5. Portal hypertensive gastropathy (PHG)

PHG, typically seen in patients with PH, is a condition of gastric mucosal ectasia and impaired mucosal defense. The incidence of PHG in patients with PH, varies greatly, ranging between 20 and 75%. Of those approximately 65–90%

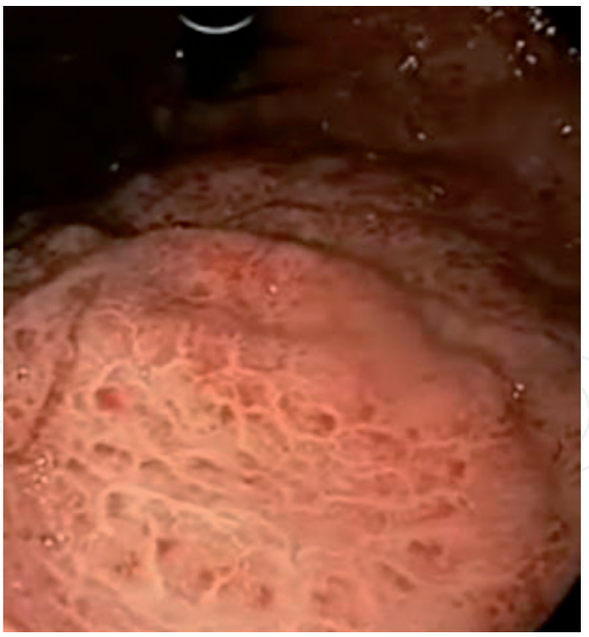


Figure 10
Severe portal hypertensive gastropathy.

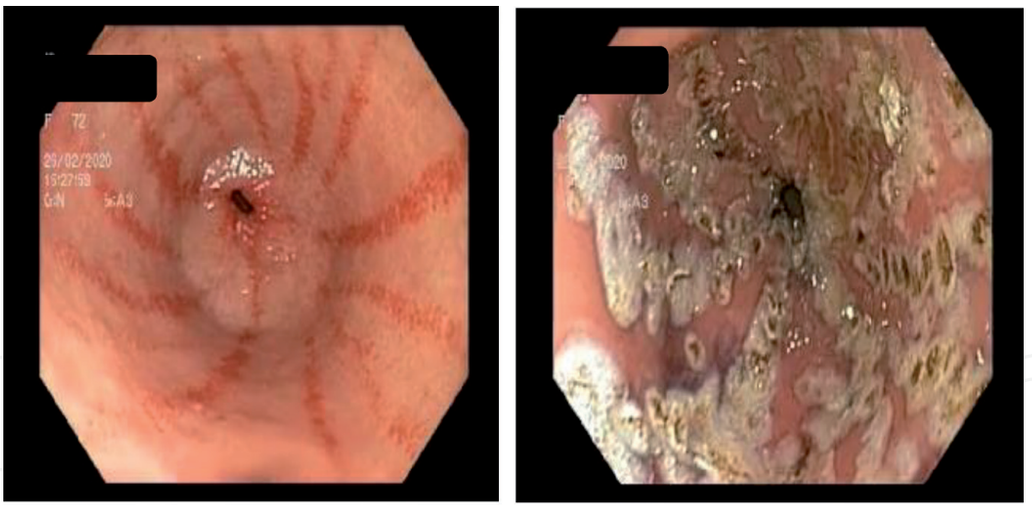
have mild PHG (mosaic pattern of the gastric mucosa without red spots), whereas 10–25% have severe PHG (mosaic pattern of the gastric mucosa with red spots; **Figure 10**) [48]. The ectatic mucosal capillaries and venules of PHG may cause recurrent bleeding, presenting as acute or chronic occult blood loss. The annual incidence of overt bleeding from mild PHG is about 5%, while it is 15% for severe PHG [49]. The frequency of rebleeding of PHG is 11–30% [50].

APC has been evaluated for the treatment of PHG, in combination with adequate NSBB. This does reduce rates of blood transfusion, ICU admission, and improve hemoglobin levels in 80–90% of patients [51, 52]. Hemospray is also an option for the treatment of active PHG bleeding. However, these endoscopic methods may be an effective bridging therapy till TIPS or liver transplant is performed [53].

6. Gastric antral vascular ectasia (GAVE)

GAVE is characterized by erythematous or raised mucosa with underlying tortuous ectatic vessels as red spots. Patterns of GAVE include honeycombing, diffuse or speckled patchy erythema, and nodular antral GAVE. These appear as diffuse or linear array in the gastric antrum **(Figure 11a**). Both PHG and GAVE may be found during endoscopy in patients with PH or discovered during variceal screening. However, in most instances, they are distinguished by their endoscopic appearance, location and when needed, biopsy for histological examination. (**Table 3**). On histology, GAVE shows presence of fibromuscular hyperplasia, fibrin microthrombi, and increased neuroendocrine cells in the lamina propria [54]. GAVE can be isolated or can be associated with cirrhosis and with systemic illnesses like scleroderma, chronic renal failure, and can occur after bone marrow transplantation. PH does not play a direct role in development of GAVE, as it is not present in up to 70% of patients, and the reduction of portal hypertension does not affect the course of the disease [55].

The endoscopic treatment includes laser photoablation, APC, radio-frequency ablation [56], EVL, and cryotherapy. APC is the most common, efficacious, and feasible therapeutic option for the treatment of GAVE **(Figure 11b),** with a reported efficacy of 90%- 100% causing a significant reduction in blood



(a) (b)

Figure 11.
Endoscopic appearance of gastric antral vascular ectasia. (a) Endoscopic appearance of gastric antral vascular ectasia, (b) appearance after argon plasma coagulation.

			Portal Hypertensive Gastropathy	Gastric Antral Vascular Ectasia
1.	Definition		PHG, typically seen in patients with PH, is a condition of gastric mucosal ectasia and impaired mucosal defense	It is characterized by erythematous or raised mucosa with underlying tortuous ectatic vessels as red spots in either a diffuse or linear array
2.	Location		Gastric fundus and body	Gastric antrum
3.	Association with Portal HTN		Always	In approximately 30% case
4.	Histology		Dliated mucosal and submucosal veins along with ectatic capillaries without microthrombi or inflammation	Fibromuscular hyperplasia, fibrin microthrombi, and increased neuroendocrine cells in the lamina propria
5.	Endoscopy		Mosaic pattern (mild) with red spots (severe)	Honeycombing, Diffuse or speckled patchy erythema, and nodular antral lesions
6.	Incidence of bleed		Low	Higher than PHG related bleed
7.	Treatment	First line	NSBB	EBL Thermocoagulation
		Second line	Thermocoagulation Liver transplantation	Cryotherapy Radiofrequency ablation Anterectomy

Table 3.
Difference between portal hypertensive Gastropathy and gastric antral vascular ectasia.

transfusion requirement [57, 58]. The setting of argon gas flow usually ranges between 0.8–2.0 L/min, the electrical power from 40 to 60 W, and, generally, a mean of 2.5 sessions are needed to achieve complete eradication [59]. Few studies have compared EVL with APC for GAVE treatment, where band ligation showed a

significantly higher rate of hemostasis, required fewer treatment sessions, a higher increase in hemoglobin values, and reduced need for blood transfusions [60, 61]. The higher efficacy EVL is attributed to a more controlled and reliable eradication of the abnormal vasculature in the mucosa and submucosa.

7. Portal hypertensive enteropathy (PHE)

PHE is a condition associated with pathologic changes and mucosal abnormalities in the small intestine of patients with PH. It is being increasingly diagnosed, due to the advent of video capsule endoscopy and deep enteroscopy. In recent studies, the prevalence of PHE varies around 93–97%, with 8–12% of patients showing evidence of ongoing bleeding [62–64]. The findings of PHE are characterized as vascular (red spots, telangiectasia, or varices) and non-vascular or inflammatory (villous edema, erythema, or polyps) changes [64] (**Figure 12a-f**).

Treatment options for PHE related bleed include glue or sclerosant for variceal bleeding and APC for non-variceal bleeding. In patients with hemodynamic instability, radiological coil embolization is an option [64].

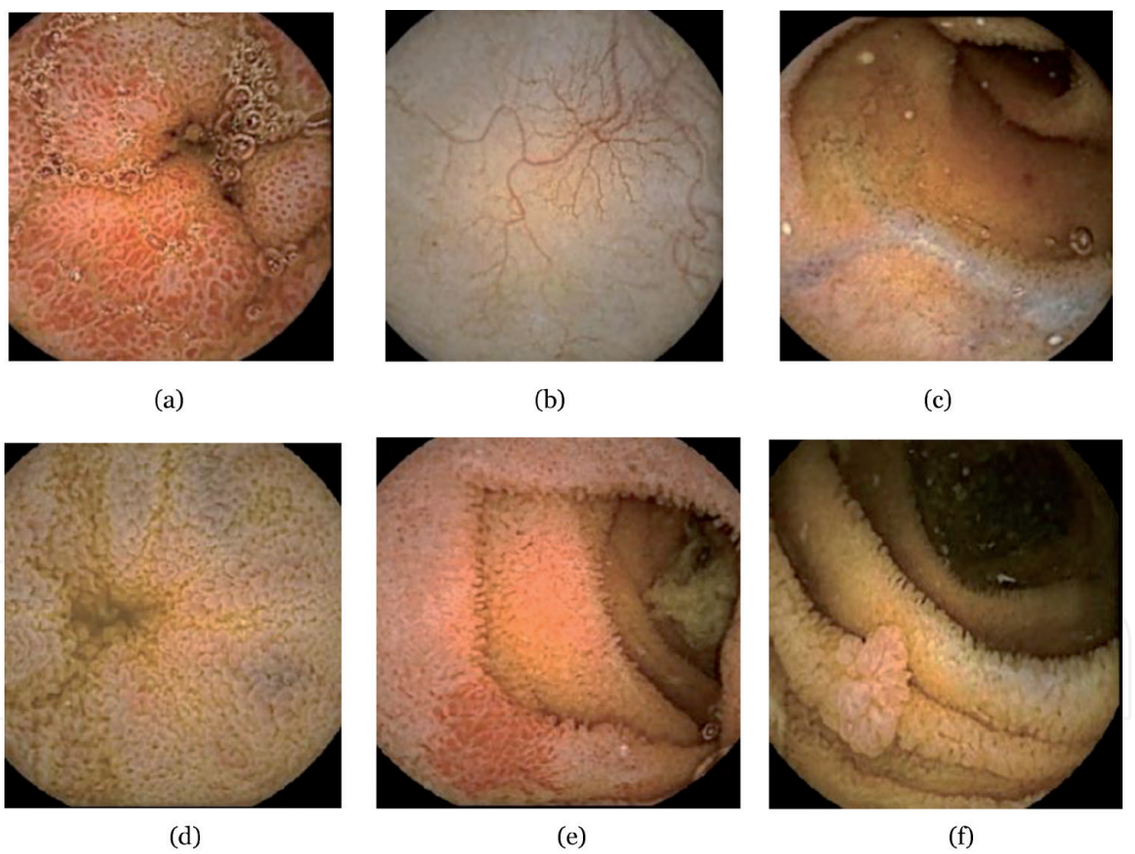


Figure 12.
Capsule endoscopy appearance of portal hypertensive enteropathy. a-c: Vascular: (a) red spot, (b) telangiectasia, (c) small intestinal varix. d-e: Inflammatory: (d) villous edema, (e) erythema, (f) polyp.

8. Portal hypertensive COLOPATHY (PHC)

Colonic abnormalities in patients with PH are referred to as PHC, and these are vascular ectasias, mosaic pattern mucosa, mucosal hemorrhages, anorectal or colonic varices, hemorrhoids, and nonspecific inflammatory changes. Its prevalence in patients with cirrhosis varies from 25 to 70%, with an estimated bleeding

rate of 0–9% [65–68]. Treatment options are ES or glue injection for variceal bleed, EVL for hemorrhoidal bleed, and APC for the non-variceal bleed and are similar to those in PHE.

9. Summary

PH can result in formation of varices at various sites with mucosal changes anywhere in the gastrointestinal tract. These can lead to acute gastrointestinal bleed or anemia. Endoscopy plays an important role in diagnosis and treatment of these complications. EVL and glue are the usual first line treatment for esophageal and GV respectively. Other therapies include sclerosant or thrombin injection, EUS-guided therapies, esophageal stent placement, APC or hemospray.

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