Treatment of Gastropathy and Gastric Antral Vascular Ectasia in Patients with Portal Hypertension

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Opinion statement

Portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) are two distinct gastric mucosal lesions that may cause acute and/or chronic upper gastrointestinal hemorrhage in patients with cirrhosis. Whereas PHG is associated with portal hypertension, GAVE may present in patients without portal hypertension or liver disease. Diagnosis is made upon visualization of the characteristic lesions with upper gastrointestinal endoscopy, although the differential may be difficult at times. PHG is characterized endoscopically by a mosaic pattern with or without red signs and a proximal distribution. PHG mainly causes chronic blood loss and anemia in patients with cirrhosis but also can cause acute hemorrhage. First-line therapy for chronic hemorrhage from PHG is a nonselective β-blocker (propranolol or nadolol) and iron supplementation. If bleeding/anemia are not controlled with these measures and the patient is transfusion-dependent, shunt therapy (transjugular intrahepatic portosystemic shunt [TIPS] or shunt surgery) should be considered. Management of acute bleeding from PHG, an infrequent event, should be accomplished with a vasoactive drug, somatostatin (or its analogues) or terlipressin. If bleeding responds, the patient must be switched to a nonselective β-blocker. Shunt therapy should be considered in patients who rebleed or continue to bleed despite adequate β-blocker therapy. GAVE is less common than PHG. It is characterized by red spots without a background mosaic pattern, typically in the gastric antrum. When lesions have a linear distribution, the lesion is called "watermelon stomach." GAVE is a cause of chronic gastrointestinal bleeding and anemia in patients with cirrhosis. If lesions are localized, first-line therapy is argon plasma coagulation. In more diffuse lesions, therapy with argon plasma coagulation is more complicated. Preliminary data suggest that cryotherapy may be a reasonable option for diffuse GAVE lesions. Neither β-blockers nor TIPS reduces the bleeding risk in patients with GAVE and thus should not be used in this setting.

Introduction

Two distinct gastric mucosal lesions occur in patients with portal hypertension: a) portal hypertensive gastropathy (PHG), which only occurs in patients with portal hypertension; and b) gastric antral vascular ectasia (GAVE), which is not exclusive to patients with portal hypertension and also occurs in patients without portal hypertension or liver disease. The only symptom associated with these lesions is upper gastrointestinal hemorrhage that is mostly chronic and is characterized by occult blood loss and anemia. Although gastroesophageal varices are the most common

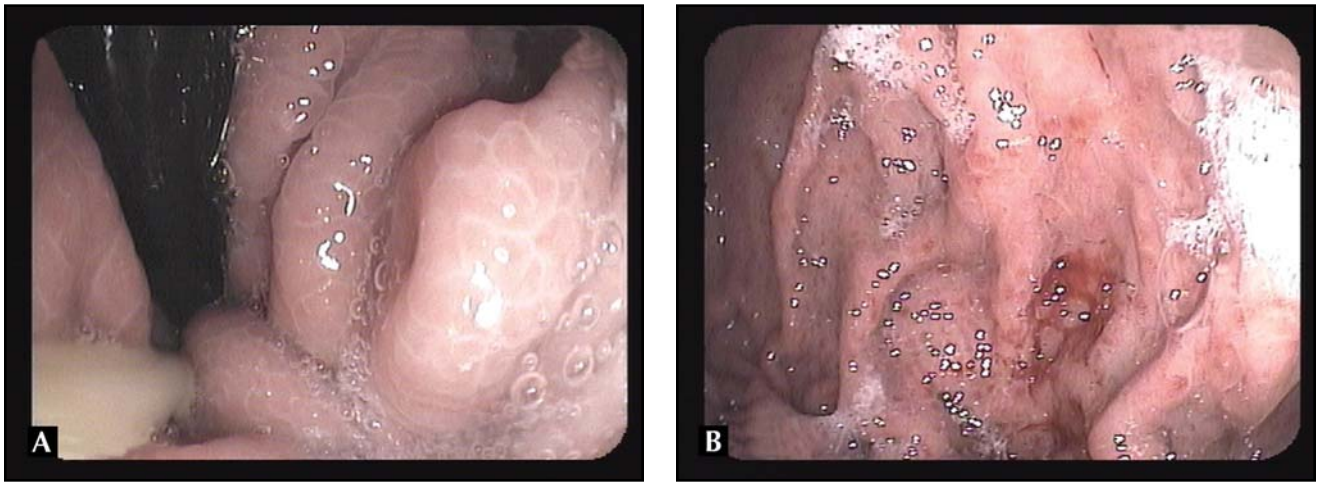

Figure 1. Portal hypertensive gastropathy (PHG). **A,** Mild PHG (notice the mosaic pattern without red spots). **B,** Severe PHG with mosaic pattern and red spots. (*Courtesy of* Dr. Pedro Menchén of the Hospital General Universitario Gregorio Marañón, Madrid, Spain.)

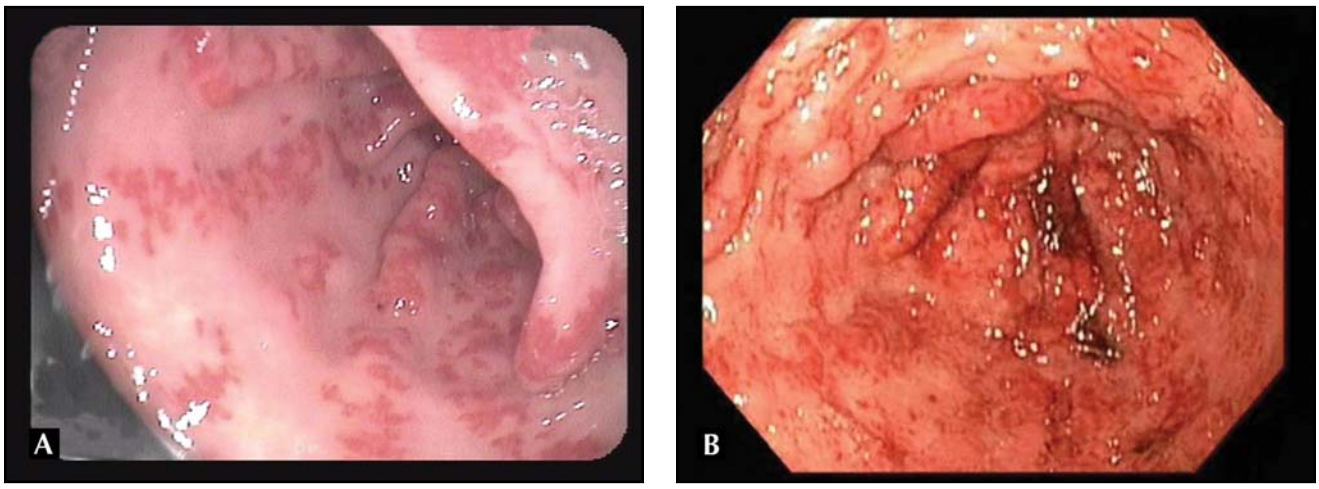

Figure 2. Gastric antral vascular ectasia. **A,** Linear lesions restricted to the antrum ("watermelon stomach"). **B,** Diffuse lesions not following a linear pattern. The appearance is similar to that of severe portal hypertensive gastropathy but without the background mosaic pattern. (*Courtesy of* Dr. Pedro Menchén of the Hospital General Universitario Gregorio Marañón, Madrid, Spain, and Dr. Louis-Michel Wong Kee Song of the Mayo Clinic, Rochester, Minnesota.)

source of acute gastrointestinal hemorrhage in patients with portal hypertension, PHG has been described as the source in up to 25% of patients [1]. As only a minority of patients with these gastric mucosal lesions present with any bleeding (chronic or acute), primary prophylaxis is not warranted, and treatment is restricted to patients who develop hemorrhage. Because therapies differ significantly between the two entities, it is important to establish an accurate diagnosis. In most cases, the diagnosis can be established endoscopically (Figs. 1 and 2); however, the differential may be difficult, particularly between severe PHG (Fig. 1B) and diffuse GAVE (Fig. 2B). A comparison of PHG and GAVE is summarized in Table 1.

PORTAL HYPERTENSIVE GASTROPATHY (PHG)

In PHG, lesions are observed mainly in the stomach's fundus. Lesions range from a subtle, mosaic-like pattern (Fig. 1A) to a mosaic pattern plus flat or slightly bulging red spots (Fig. 1B). Several grading systems quantify the endoscopic lesions' severity from mild to severe [2–5]. In general, a mosaic pattern alone is graded as "mild" PHG, whereas in "severe" PHG, superimposed red spots are present. Not unexpectedly, patients with severe PHG are more likely to bleed [6,7]. Similar lesions can be observed in the small bowel and colon, and although they may lead to gastrointestinal hemorrhage, the frequency of acute and chronic hemorrhage due to these lesions remains to be determined [8–11].

PHG's prevalence is associated with the histologic and biochemical severity of liver disease [12]. Recently, PHG's prevalence in patients with chronic hepatitis C and advanced liver fibrosis was established at 37%, with it being severe in 3% of the patients [13•]. In more advanced liver disease, PHG's prevalence varies between 51% and 98% [1,4,12].

Table 1. Comparison of PHG and GAVE

	PHG*	GAVE*
Associated with portal hypertension	Always	Not always (also present in other diseases)
Distribution in stomach	Proximal	Distal
Mosaic pattern	+	–
Red spots	+	+
Pathology		
Thrombi	–	+++
Spindle cell proliferation	+	++
Fibrohyalinosis	+	+++
Response to therapies directed at decreasing portal pressure	+	–
First-line treatment		
Acute	Octreotide/somatostatin	Endoscopic ablation
Chronic	Propranolol	Endoscopic ablation
Salvage therapy†	TIPS/shunt surgery	Antrectomy and Billroth I

*Plus signs indicate presence, whereas minus signs indicate absence.
†To be evaluated on an individual basis.
GAVE—gastric antral vascular ectasia; PHG—portal hypertensive gastropathy; TIPS—transjugular intrahepatic portosystemic shunt.

Histologically, PHG is characterized by the presence of dilated capillaries and venules in the mucosa and submucosa without erosion, inflammation, or fibrinous thrombi [3]. The key pathogenic factor is the presence of portal hypertension, which produces venous congestion in the gastric mucosa. This is further supported by the fact that PHG correlates with the presence/size of varices [1], as well as the reported increased incidence of PHG, or the worsening of previous PHG after variceal eradication by sclerotherapy or endoscopic variceal ligation (EVL) [14–18]. However, it appears that the PHG that develops after variceal eradication is only transient [1,7,18].

The main complications related to PHG are acute and chronic upper gastrointestinal hemorrhage. Acute hemorrhage incidence from PHG is usually very low and observed mainly in patients with more severe PHG [12]. The more common presentation of gastrointestinal hemorrhage secondary to PHG is chronic, slow bleeding with resultant anemia. The frequency of chronic bleeding is difficult to estimate (30%–60% in severe PHG and 0%–30% in mild PHG) [6]. In the largest series of patients with PHG followed for a mean period of 18 months, acute bleeding occurred in 2.5% of the cases, whereas chronic bleeding occurred in 11% [1]. In a prospective study of primary prophylaxis of variceal hemorrhage in patients with varices, acute bleeding from PHG occurred in 6% of the cases (compared with 22% of variceal hemorrhage cases) in a mean follow-up period of 16 months [19].

Diagnosis of bleeding PHG is established when diffuse oozing from lesions is observed or when no other causes of acute or chronic gastrointestinal bleeding can be identified after thorough gastrointestinal tract evaluation. The initial management of PHG is with iron supplementation and nonselective β-blockers. Propranolol is the specific nonselective β-blocker that has been investigated in treatment of bleeding PHG. This drug was first evaluated in the prevention of recurrent bleeding from gastropathy in an open trial of patients who had had acute bleeding from severe PHG. Almost all (13 of 14) patients achieved control of the acute bleeding episode [20]. This drug's efficacy in preventing rebleeding was demonstrated in the classic randomized controlled trial evaluating propranolol's role in preventing recurrent bleeding in severe PHG [21]. Compared with placebo, patients who received propranolol had a significantly lower rebleeding rate at 12 months (35% vs 62%) and at 30 months (48% vs 93%). Furthermore, a trial by Lo et al. [22] showed that propranolol ameliorates post-EVL PHG. If the bleeding is controlled with nonselective β-blockers, medical treatment may be continued. If the patient continues to bleed but is not transfusion-dependent, β-blockers and iron therapy can be continued with occasional blood transfusions, as needed. However, if the patient continues to bleed and is transfusion-dependent, shunt therapy (transjugular intrahepatic portosystemic shunt [TIPS] or shunt surgery, depending on local expertise and patient characteristics) is indicated.

Vasoactive drugs such as somatostatin and its analogues (octreotide, vapreotide) and vasopressin and its analogue, terlipressin, which are effective in the context of acute variceal hemorrhage mostly through a portal pressure–lowering effect, theoretically could be effective in the setting of bleeding due to PHG. Two trials have evaluated the effect of these vasoactive drugs in acute hemorrhage from PHG [23,24]. In both trials, acute

bleeding from PHG ceased in all patients who received somatostatin [24] or octreotide [23,24]; however, vasopressin was not more effective than omeprazole [23]. One study has evaluated the use of two different doses of terlipressin in the setting of acute bleeding from gastroesophageal varices or PHG [25]. Of 16 patients who had acute bleeding from PHG, seven were randomized to the higher dose of terlipressin (1 mg/4 h intravenously), whereas nine were randomized to the lower dose (0.2 mg/4 h intravenously) during 5 days. The study's main endpoint was 5-day hemostasis. All patients randomized to the higher dose achieved 5-day hemostasis, compared with seven of nine randomized to the lower dose, suggesting that the higher dose may be more effective.

From a rational point of view, it seems more practical to start therapy for acute bleeding from PHG with a safe vasoactive agent, namely terlipressin or somatostatin and analogues, rather than β-blockers. In fact, current recommendations state that pharmacologic therapy (somatostatin or its analogues, octreotide and vapreotide) or terlipressin should be initiated as soon as variceal hemorrhage is suspected and prior to diagnostic endoscopy [26]. As acute bleeding from PHG presents in the same way as variceal hemorrhage and may be as severe [12], it follows that this pharmacologic therapy would have been initiated in these patients on presentation, and because bleeding from PHG has the same pathophysiology as variceal hemorrhage, administration of these drugs should continue for 3 to 5 days as recommended for variceal hemorrhage [26]. In case these agents do not control bleeding entirely (ie, the patient progresses to a more chronic bleeding), propranolol treatment may be initiated and titrated to the maximum tolerated dose.

Other pharmacologic agents that have been reported in PHG management are losartan [27], thalidomide [28], and corticosteroids [29]. However, these are small, open-label studies [27] or case reports [28,29], so these data must be interpreted with caution.

As per chronic bleeding from PHG, in patients in whom the episode of acute hemorrhage remains unresponsive to pharmacologic therapy, more invasive therapeutic options exist. Endoscopic treatment of these lesions is not effective. However, TIPS placement or shunt surgery that lowers or even normalizes portal pressure has been effective in almost all cases [30–34]. The choice between TIPS or surgery should be made on an individual basis.

GAVE

GAVE is characterized by red spots without a background mosaic pattern. The lesions typically are in the antrum. If these red spots are aggregated in a linear distribution, the term "watermelon stomach" is used (Fig. 2A). When the red spots are diffusely distributed in the distal and the proximal stomach, the term "diffuse gastric vascular ectasia" is preferred (Fig. 2B). Although these lesions are observed most frequently in patients with cirrhosis and portal hypertension, they also have been observed in patients with autoimmune disease and bone marrow transplantation. The exact pathophysiologic mechanism that underlies this condition in patients with liver disease is unknown, although it has been associated with NSAID use [13•]. Unlike PHG, GAVE's pathophysiology apparently does not involve portal hypertension, as bleeding from these lesions does not respond to portal pressure–reducing therapies. However, given case reports of GAVE resolution after liver transplantation, liver insufficiency has been implicated in its pathophysiology [35,36].

Histologically, GAVE is clearly distinct from PHG. Dilated mucosal capillaries with fibrin thrombi and fibromuscular hyperplasia of the lamina propria without signs of inflammation may be observed [37], as may be spindle cell proliferation and fibrohyalinosis. However, biopsies are rarely deep enough to distinguish between these two entities. From a clinical perspective, its presentation is similar to that of PHG, as it may cause acute or chronic bleeding and iron deficiency anemia. A study that evaluated the treatment outcomes and endoscopic appearance of GAVE identified this entity in 4% (26 of 744) of patients with nonvariceal upper gastrointestinal bleeding. Of these 26 patients, eight also had portal hypertension [38]. First-line therapy for symptomatic anemia related to GAVE is iron replacement and, if necessary, packed red blood cell transfusions. Specific therapy for GAVE is mainly endoscopic. If lesions are localized, first-line treatment is thermoablative therapy, such as argon plasma coagulation (APC) [38–42,43•], heater probe [37], and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser coagulation, all of which have been shown to reduce rebleeding and transfusion requirements [44–46]. Given that heater probe and Nd:YAG have a deeper effect and have been related to perforation [45], APC therapy is preferred. However, APC is not ideal for treating diffuse GAVE, as it necessitates long, intensive sessions. In recent years, cryotherapy has been used to treat bleeding mucosal vascular lesions, including GAVE. In a series of 26 patients with actively bleeding diffuse mucosal lesions of the gastrointestinal tract, of which seven corresponded to "watermelon stomach," hemorrhage cessation was observed in five (71%) of the cases [47]. In another series of nine patients with bleeding GAVE, eight of whom had failed APC, six (67%) had a complete response (raising hemoglobin without transfusion requirement) [48]. Cryotherapy offers the advantage of treating large areas of the mucosa relatively quickly and should be considered in patients with diffuse lesions or in those who do not respond to APC.

Pharmacologic therapeutic options for treating GAVE are limited. Pilot studies suggest that estrogen–progesterone may be useful [49] and should be attempted when endoscopic therapy fails. Similarly, there are some case reports of the successful use of tranexamic acid, an antifibrinolytic agent [50,51], and thalidomide [52]. There have been controversial case reports about octreotide's effect in GAVE [53,54]; therefore, this is not recommended.

In extreme cases in which combination endoscopic/pharmacologic therapy is unsuccessful, surgery with antrectomy may be considered on an individual basis [55–57]. TIPS does not reduce the bleeding from GAVE and should not be placed in these patients [34]. As mentioned previously, there have been three case reports showing reversal of GAVE after liver transplantation. However, the data are insufficient to recommend this therapy unless the patient is otherwise a liver transplant candidate [35,58].

Treatment

PHG

Diet and lifestyle

- Any restrictions in diet and lifestyle are determined mainly by the underlying liver disease. Importantly, absolute alcohol abstinence is recommended. Iron supplementation should be administered in the case of iron deficiency anemia. NSAIDs should be avoided in the general management of all patients with cirrhosis.

Pharmacologic treatment: general principles

- The main goals of pharmacologic therapy in PHG are to control an episode of acute bleeding, prevent a recurrent episode of acute hemorrhage, and eliminate or decrease chronic bleeding from these lesions. Success or failure of a therapeutic approach is determined according to the clinical setting. In the setting of acute hemorrhage, treatment success should be determined by control of the acute episode as determined by hemodynamic stability and transfusion requirement cessation and by prevention of a recurrent episode. In the setting of chronic hemorrhage, treatment success should be determined by elimination of or a reduction in transfusion requirements. If pharmacologic therapy is not successful, more invasive approaches should be evaluated individually.

Somatostatin and analogues

Somatostatin is a hormone produced in the hypothalamus that inhibits the release of hormones such as adrenocorticotropic hormone, glucagon, insulin, and growth hormone. It also inhibits the release of enzymes such as pepsin, rennin, secretin, and gastrin. It produces direct vasoconstriction of the splanchnic vascular bed, leading to portal venous inflow reduction and, therefore, portal pressure reduction. The portal hypotensive effect has been demonstrated in patients with cirrhosis [59].

Octreotide is a synthetic octapeptide that mimics the properties of the natural hormone somatostatin. It is an important inhibitor of growth hormone, glucagon, and insulin (more so than somatostatin). It also suppresses the luteinizing hormone response to gonadotropin-releasing hormone; decreases splanchnic blood flow; and inhibits the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. Octreotide's portal pressure–reducing effect seems to be transient [60,61], although a recent study has shown a portal hypotensive effect of long-acting octreotide after 3 months of administration [62].

Neither octreotide nor somatostatin is approved by the US Food and Drug Administration (FDA) for treating acute bleeding from PHG.

Standard dosage Octreotide: 100-μg bolus followed by a continuous infusion of 50 μg/h; somatostatin: 250-μg bolus followed by a continuous infusion of 250 (or 500) μg/h.

Contraindications	Sensitivity to the drug or any of its components.
Main drug interactions	Decrease in cyclosporin levels. Patients receiving insulin, oral hypoglycemic agents, β-blockers, calcium-channel blockers, or diuretics may require dose adjustment.
Main side effects	Gastrointestinal symptoms, hyper- or hypoglycemia, hypothyroidism, dizziness, nausea. Long-term use may lead to biliary stone or sludge development; however, this is unlikely to occur in the acute setting.
Special points	Although not tested in PHG, doubling the dose of somatostatin infusion (to 500 μg/h) has been shown to be more effective in reducing portal pressure and in controlling hemorrhage from gastroesophageal varices. This can be attempted when acute bleeding from PHG does not respond to the lower dose [60,63].
Cost effectiveness	There are no data about these drugs' cost effectiveness in the setting of PHG.

Terlipressin

	Terlipressin is a vasopressin analogue that acts mainly on the V1a receptor, leading to arteriolar vasoconstriction and thereby to splanchnic vasoconstriction and a reduction in portal pressure and an increase in systemic vascular resistance, blood pressure, and glomerular filtration rate [61,64]. This drug is not FDA-approved.
Standard dosage	1 to 2 mg intravenously every 4 hours.
Contraindications	Previous history of severe ischemic events.
Main drug interactions	The combination of terlipressin with other drugs that also can induce bradycardia, such as propofol, may induce greater bradycardia.
Main side effects	Ischemic events. It also may produce a decrease in heart rate and a slight increase in blood pressure, skin pallor (from skin vasoconstriction), hypokalemia, and bronchial constriction.
Cost effectiveness	There are no data about these drugs' cost effectiveness in the setting of PHG.

Nonselective β-adrenergic blockers

	Nonselective β-blockers (propranolol, nadolol) combine β1 and β2 antagonisms that result in portal pressure reduction due to the negative chronotropic and inotropic effect (β1 blockade) and allow alpha vasoconstriction in the splanchnic territory (β2 effect). This last effect is most important; therefore, selective β1 blockers are suboptimal. These pharmacologic agents constitute the mainstay of therapy in patients with bleeding PHG. These drugs require proper dosage titration to maximal tolerance, as no correlation exists between reduction in heart rate, dose, or plasma level and their portal pressure–reducing effect. Baseline electrocardiogram should be done before administration to exclude heart blocks. These drugs are not FDA-approved for this indication. Propranolol is the prototype nonselective β-blocker used to treat PHG [21]. Propranolol hydrochloride is a synthetic β-receptor–blocking agent that competes with other β-receptor–stimulating agents for available receptors. Nadolol, another nonselective β-blocker, also has been used in this setting. Its main advantage over propranolol is a longer half-life (allowing once-daily administration) and, possibly, a better tolerance.
Standard dosage	Standard initial dosage of propranolol is 20 mg orally twice daily, which should be progressively increased to 160 mg twice daily, the maximum tolerated dose, or until heart rate is reduced to 50 to 55 bpm. Standard initial dosage of nadolol is 20 mg orally once daily, which should be similarly increased to 160 mg or the maximum tolerated dose.

Contraindications	Propranolol is contraindicated in cardiogenic shock, sinus bradycardia and greater than a first-degree atrial-ventricular block, bronchial asthma, and congestive heart failure (unless it is secondary to a tachyarrhythmia that is treatable with propranolol).
Main drug interactions	Special caution should be taken when administering simultaneously with cathecholamine-depleting drugs and calcium-channel blockers, as the effect of these drugs may add on to propranolol's effect. There also may be interaction with glucose metabolism that may require adjustment of oral antidiabetic drugs or insulin. Furthermore, it also may mask hypoglycemia symptoms. Ethanol and aluminium hydroxide gel slow the rate of intestinal absorption of propranolol.
Main side effects	The most common side effects related to β-blockers in cirrhosis are lightheadedness, fatigue, and shortness of breath. Although some disappear with time or after dose reduction, treatment withdrawal is necessary in 15% of patients. Trials in which nadolol was used have reported lower side effect rates (~ 10%) than those involving propranolol (~ 17%); however, direct comparisons have not been performed. Side effects are reversible upon drug discontinuation [65].
Special points	Sudden increases in portal pressure with the subsequent increases in portal hypertensive–related complications have been described with sudden discontinuation of β-blockers. Therefore, discontinuation should be gradual.
Cost effectiveness	There are no data evaluating propranolol or nadolol's cost effectiveness in the context of PHG.

Invasive therapeutic options

- The aim of surgery or TIPS in PHG is to control acute or chronic bleeding that has not responded to adequate pharmacologic therapy and that requires frequent transfusions. The choice between TIPS or shunt surgery is determined by the underlying liver disease and local expertise.

TIPS

Standard procedure	TIPS consists of the creation of an artificial shunt between a branch of the intrahepatic portal vein and a branch of the hepatic vein that is maintained patent by expandable metal stent placement. Recently, the use of expanded polytetrafluoroethylene (ePTFE)–covered stent grafts seems to offer better outcomes due to a lower shunt dysfunction rate [66]. From a functional perspective, TIPS is like a side-to-side surgical portacaval shunt but does not require general anesthesia or major surgery.
Contraindications	Contraindications to TIPS placement include right heart failure, pulmonary hypertension, severe liver dysfunction with severe hepatic encephalopathy, and jaundice [67].
Complications	Hepatic hematoma, liver capsule rupture, extrahepatic portal vein puncture, hemobilia, shunt dysfunction with possible recurrence of portal hypertensive–related complications, portosystemic encephalopathy, liver failure, and increased susceptibility to bacteremia [67]. Increased hepatocellular carcinoma incidence after the placement of bare stents has been described [68].
Special points	Bare stents have a high rate of shunt dysfunction development. The ePTFE–covered stent grafts prevent hepatic tissue growth into the shunt and are associated with a significantly lower dysfunction rate [69]. Shunt patency should be monitored with serial Doppler sonography or angiography.
Cost effectiveness	No studies have evaluated the cost effectiveness of using TIPS as salvage therapy in bleeding from PHG that has not responded to pharmacologic therapy.

Surgical portocaval shunt

Standard procedure	This method decompresses the portal system by diverting the blood from the portal vascular bed toward the caval venous system. After the surgery, the liver perfusion relies more on the hepatic arterial perfusion, although the proportion may vary according to the surgical technique. The election of the shunt to use depends on the patient's situation, the possibilities of liver transplantation, and the surgical team's expertise.
Contraindications	Surgery has contraindications similar to those of TIPS placement, including right heart failure, pulmonary hypertension, severe liver dysfunction with severe hepatic encephalopathy, and jaundice.
Complications	Postoperative liver failure, portosystemic encephalopathy, shunt thrombosis, and all the complications associated with major surgery.
Cost effectiveness	No studies are available about the cost effectiveness of surgery versus TIPS in the context of PHG.

GAVE

Diet and lifestyle

- Any diet and lifestyle restrictions are mainly determined by the underlying disease. If GAVE is associated with liver disease, the importance of absolute alcohol abstinence should be emphasized. Iron supplements should be administered in the case of iron deficiency anemia. Avoidance of NSAIDs in patients with underlying chronic hepatitis C [13•] and other chronic liver diseases may be recommended.

Pharmacologic treatment

- As in PHG, the main goal of therapy in GAVE is to control acute and chronic hemorrhage from these lesions and to prevent their recurrence. The success or failure of a therapeutic approach should be determined by the patient's clinical course. Pharmacologic treatment of GAVE has not been evaluated in well-designed, randomized controlled trials and should be considered exclusively in patients who do not respond to first-line endoscopic therapy.

Estrogen progesterone

Standard dosage	Ethinyl estradiol, 30 μg orally daily, and norethindrone acetate, 1.5 mg orally daily.
Contraindications	Thromboembolic disorders, cerebrovascular or coronary artery disease, diabetes with vascular complications, major surgery with prolonged immobilization, known or suspected carcinoma of the breast or endometrium, abnormal genital bleeding, hepatic adenomas or carcinomas, known or suspected pregnancy, cholestatic jaundice of pregnancy, or jaundice with prior use.
Main drug interactions	Concomitant use of rifampin, barbiturates, phenylbutazone, phenytoin, griseofulvin, ampicillin, or tetracyclines.
Main side effects	Headaches, vaginal candidiasis, upper respiratory infection, nausea, menstrual cramps, breast tenderness, sinusitis, vaginitis, abnormal cervical smear, acne, urinary tract infection, mood swings, weight gain, vomiting, and metrorrhagia in women.
Special points	It does not improve appearance of endoscopic lesions.
Cost effectiveness	There are no data evaluating the cost effectiveness of estrogen progesterone in GAVE.

Endoscopic treatment

- The first-line treatment in GAVE is endoscopic ablation of the lesions. The main aim of therapy is to control acute bleeding and to eliminate chronic bleeding from these lesions. Multiple treatment sessions typically are required to achieve the therapeutic goal. In the case of localized lesions, thermoablative therapy—mainly APC—is indicated. In diffuse lesions, cryotherapy may be an option. Success or failure is determined by stabilization (or not) of hematocrit and transfusion requirement. Choice of endoscopic therapy modality depends on the experience and availability at each center.

APC

Standard procedure	APC produces a noncontact thermal coagulation by applying high-frequency electric current that is passed through argon gas. The settings for electrical power and argon gas flow vary widely among studies, from 20 to 80 W for electrical power (median ~ 50 W) and flows between 0.5 and 2.0 L/min (median ~ 1 L/min), although the ideal settings are the lowest necessary to achieve satisfactory coagulation. The technique usually is a combination of focal pulse and "paint brush," with the goal of obliterating 90% of the vascular lesions. Repeat procedures (in 2–6 weeks) depend on control (or recurrence) of gastrointestinal hemorrhage as evidenced by hematocrit, need for transfusions, overt macroscopic hemorrhage, and endoscopic goal achievement. APC has an advantage over other procedures in that it does not need a perpendicular approach and that it is relatively safe (limited depth of coagulation) [70]. It also has the advantage of being able to treat large surface areas of the mucosa in a single session.
Complications	Perforation, bleeding, aspiration, and thermal ulcer formation.
Special points	APC has a lower risk of perforation compared with Nd:YAG laser, although more sessions are required. Furthermore, it is fairly easy to use, as it is not necessary to have a perpendicular position relative to the mucosa.
Cost effectiveness	Overall, APC is less expensive than Nd:YAG, as the unit and the fibers are less expensive, and it requires less set-up time. However, more sessions may be required. No data are available regarding APC's cost effectiveness in the context of GAVE.

Nd:YAG

Standard procedure	Nd:YAG laser increases the local temperature and produces proteic degradation and coagulation. It is positioned approximately 1 cm from the mucosal surface and is used with a power setting between 40 and 90 W, with pulse duration of 0.5 to 1 seconds. The lower the power, the lower the risk of perforation, although the number of sessions required will increase. As for APC, Nd:YAG laser has the advantage of being able to treat large surface areas of the mucosa in a single session. Therapy is repeated every 2 to 4 weeks until the therapeutic goal is achieved and the patient has stable hemoglobin levels.
Complications	Perforation, bleeding, aspiration, and thermal ulcer formation.
Special points	Sucralfate may be used prophylactically to reduce thermal ulcer formation risk. Nd:YAG laser achieves a hemostatic response earlier than APC, although the risk of perforation may be greater.
Cost effectiveness	There are no data that evaluate Nd:YAG laser therapy's cost effectiveness in the context of PHG.

Heater probe

Standard procedure	The heater probe coagulates the tissue with a thermal element that heats the device tip. As with the other ablation techniques, more than one session is required to achieve hemostasis.

Complications	Perforation, bleeding, aspiration, and thermal ulcer formation.
Special points	The heater probe has the disadvantage of not being able to cover as large a surface area as the Nd:YAG laser and APC.
Cost effectiveness	No data are available regarding this endoscopic modality's cost effectiveness in the setting of GAVE.

Cryotherapy

Standard procedure	A rapid expansion with compressed nitrous oxide results in a decrease in temperature, causing freezing of the mucosa. The tip of the cryospray catheter is placed 2 to 3 cm from the endoscope tip, and the cryogenic spray is applied to the mucosal lesions until the mucosa appears whitened and ice is formed (3–4 seconds). Endoscopy should be repeated every 2 to 3 days and applied again until all lesions are fully treated [47]. An overtube for gas ventilation may be used [48].
Complications	One case of transient abdominal pain has been described [47].
Special points	This therapeutic option seems to be effective in treating diffuse lesions refractory to APC [48].
Cost effectiveness	No data are available regarding this endoscopic modality's cost effectiveness in the setting of GAVE.

Surgery

- The surgical approach is restricted to cases of refractory bleeding in which endoscopic and/or pharmacologic therapeutic approaches have failed. Before turning to surgery, a thorough endoscopic evaluation of the gastrointestinal tract should be performed to exclude other causes of bleeding. The use of shunt procedures such as TIPS or side-to-side surgical shunts have not proven effective in the surgical treatment of GAVE and should not be used [34]. Antrectomy with Billroth I anastomosis is the procedure of choice [55,57].

Antrectomy with Billroth I anastomosis

Contraindications	Contraindications depend on each patient's baseline status.
Complications	Complications also depend on each patient's baseline status and the surgical procedure itself. Patients with cirrhosis—even those with compensated disease—who undergo major intra-abdominal surgery can develop decompensation.
Special points	This surgical approach offers the most definitive therapy for GAVE, with low rates of rebleeding and anemia. However, due to comorbid illnesses and advanced age that are typically associated with this entity, this therapeutic option should be used only as a salvage therapy when all other options have failed, and with proper counseling of the patient.
Cost effectiveness	No studies have evaluated this approach's cost effectiveness in GAVE.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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