Chapter 5

Portal Hypertensive Gastropathy (PHG)

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Additional information is available at the end of the chapter

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Abstract

Reversal of erosive gastritis in patients with portal hypertension by surgical shunts evolves the term of portal hypertensive gastropathy. In 1984, Sarfeh et al. addressed the term PHG to describe the distinctive erosive gastritis in patients with portal hypertension. Since that time, the recorded incidence of PHG in the studies has varied widely from 20 to 75% in patients with portal hypertension, with or without liver cirrhosis. As the underlying pathophysiology of the disease is unclear, not all the patients with portal hypertension developed PHG. Thus, portal hypertension cannot be the only factor for the development of PHG. Patients with PHG presented with either acute or chronic bleedings. Acute presentation is an emergency case. Anemia from chronic bleeding is a frequent presentation in PHG patients. The diagnosis is confirmed by a characteristic endoscopic appearance of PHG. Capsule endoscopy and dynamic CT are also used for the diagnosis of PHG. The goal of the treatment of PHG is reducing the portal pressure in patients with acute or chronic bleeding. Pharmacological treatment, endoscopic therapy, trans-jugular intrahepatic portosystemic shunt (TIPS), and shunt surgery are different modalities for treatment of PHG. Yet, primary prophylaxis treatment is not recommended in the patients with PHG.

Keywords: portal hypertensive gastropathy, portal hypertension, gastropathy, GAVE, liver cirrhosis

1. Introduction

1.1. Definition

Portal hypertensive gastropathy (PHG) is a painless condition of gastric mucosal ectasia and impaired mucosal defense, typically seen in patients with portal hypertension [1].

Portal hypertension (PH) exists when the hydrostatic pressure in the portal vein or its branches has increased. Two important factors are implicated; vascular resistance and

blood flow, thus if the pressure gradient anywhere along the portal venous system (between the portal vein, and hepatic veins or the inferior vena cava (IVC)) is increased, portal hypertension develops.

The normal portal venous pressure ranges from 5 to 10 mm Hg, therefore, if the hepatic venous pressure gradient (HVPG) is ≥10 mm Hg, significant portal hypertension is considered, but if the HVPG is ≥12 mm Hg, severe portal hypertension is diagnosed [2].

The causes of portal hypertension are classified into three categories related to anatomical consideration. First, are causes originating in the portal venous system before it reaches the liver (pre-hepatic), e.g. portal vein thrombosis, schistosomiasis, primary biliary cholangitis/primary sclerosing cholangitis, or congenital hepatic fibrosis. Second, are causes within the liver (intrahepatic) e.g. cirrhosis as a result of viral, non alcoholic fatty liver disease (NAFLD), or autoimmune. Finally, are causes between the liver and the heart (post-hepatic) e.g. Budd-Chiari syndrome, inferior vena cava obstruction, or hepatic veno-occlusive disease (**Table 1**). The most common cause of PH is cirrhosis [3].

1.2. Essentials to diagnose PHG

- Portal hypertension with or without cirrhosis.
- Characteristic endoscopic findings.

Prehepatic	Hepatic	Posthepatic
Portal vein thrombosis	Cirrhosis of any cause, e.g. chronic viral hepatitis, alcoholic, autoimmune, NAFLD, biliary atresia, etc.	Inferior vena cava obstruction
Arteriovenous fistula	Primary biliary cholangitis	Hepatic vein thrombosis
Splenomegaly	Primary sclerosing cholangitis	Budd-Chiari syndrome
	Schistosomiasis	Right sided heart failure, e.g. from constrictive pericarditis
	Congenital hepatic fibrosis	
	Nodular regeneration hyperplasia	
	Granulomatous or infiltrative diseases (Gaucher, sarcoidosis, amyloid deposition	
	Toxicity (from arsenic, copper, methotrexate, amiodarone, ….)	
	Veno-occlusive disease	

NAFLD, non alcoholic fatty liver disease.

Table 1. Condition associated with portal hypertension.

2. History

In 1984, Sarfeh et al. recognized a distinct form of gastric mucosal hemorrhage in patients who had portal hypertension, they called it "portal hypertensive gastritis". They reported that this mucosal lesion in patients with portal hypertension was reversed after the portacaval shunt, in contrary to the mucosal lesion of patients without portal hypertension. Therefore, they concluded that there is a unique mucosal change excited with portal hypertension. 1 year later, it was discovered that this mucosal change was not a form of gastritis as there is no evidence of inflammation in the mucosa. Specific histopathological findings described this change, and the term "portal hypertensive gastropathy" was introduced by McCormack et al. in 1985 as a separate entity. However, there was no grading system of the endoscopic findings to put an accurate score for this condition. Several grading systems like the three- category system, and the two-category system have been proposed in 1994. The clinical importance of grading classification system resides in the fact that patients with severe PHG have a higher chance to bleed than patients with mild PHG [4].

The overall mortality from gastrointestinal bleeding is up to 25% of the mortality in patients with cirrhosis. In recent years however, PHG has been recognized as a distinct entity of gastrointestinal bleeding in patients with cirrhosis and portal hypertension. While variceal hemorrhage and peptic ulcer disease are known as significant causes of GI bleeding in cirrhosis, PHG and gastric antral vascular ectasia (GAVE) should also be considered as important causes. However, PHG should be differentiated from GAVE, GAVE occurs in patients with cirrhosis and portal hypertension, in addition to other conditions, such as chronic renal failure, connective tissue disorders, and bone marrow transplantation. On the other hand, PHG occurs only in patients with portal hypertension, whether with or without cirrhosis. In patients with cirrhosis, PHG is more common than GAVE [5].

However, although the endoscopic, histological and hemodynamic features of PHG mucosa have been extensively studied, the pathogenesis of PHG is still poorly understood, its natural history is not clearly documented and its treatment needs to be improved [6].

3. Epidemiology

The incidence of PHG varies greatly, it ranges between 20 and 75% of patients with portal hypertension, of those, approximately 65–90% have mild PHG, whereas 10–25% have severe PHG. This wide discrepancy in results may be attributed to the fact that the study was carried out on different groups of patients; patients with cirrhosis, patients without cirrhosis, patients with different Child-Pugh score of liver failure, and lastly patients with history of previous esophageal eradication therapy [7]. It was noticed that higher prevalence of PHG is found in patients with severe portal hypertension, advanced liver disease, and post-eradication therapy of esophageal varices [8]. Conversely, the incidence of acute gastrointestinal bleeding (hematemesis and/or melena) in PHG patients with cirrhosis were low; reported incidences ranged from 2.5 to 30%, with the greatest occurrences being observed in patients with severe PHG [9].

On the other hand, PHG as a marker of portal hypertension has conflicting results among the studies. Its sensitivity, positive predictive value (PPV) and negative predictive value (NPV), vary considerably between the studies, but its specificity has been reported to be above 95%. Snake-skin pattern has higher specificity (93–100%) for the diagnosis of PHG [10].

PHG can present at any age, including pediatric or adult patients [7].

4. Pathophysiology

The pathogenesis of PHG is still poorly understood. Portal hypertension is essential in the presence of PHG, due to the mechanical effect of the increased pressure in the portal vein which leads to hyper-dynamic congestion with a net increase in the gastric blood flow, this increase occurs in the submucosal, muscle, and serosal layers, while decreasing in the mucosal layer due to congestion and stasis. These hemodynamic changes impair gastric mucosal defense mechanisms, which lead to release of pro-inflammatory mediators, and alter the growth factors which render gastric mucosa more susceptible to injury, and impair mucosal healing. This defenseless mucosa may explain the increase in the rate of bleeding from PHG, additionally this abnormal gastric microcirculation, may render gastric mucosa more vulnerable to hypoxia, and more susceptible to noxious gastric factors, such as aspirin and ethanol [4].

Many other factors have also been implicated in the pathogenesis of PHG such as increased production of nitric oxide (NO), oxygen free radicals, endothelin-1, tumor necrosis factor-α, and prostaglandins. The most important factor, NO, is a potent vasodilator secreted by endothelial cells which may underlie the gastric vascular dilation and hyper-dynamic circulation in PHG. Furthermore, the expression of transforming growth factor α (TGF-α) and the epidermal growth factor (EGF) receptors in the gastric mucosa were reported to be highly elevated in areas of spontaneous gastric injury. Recently, studies found other factors, like p53-upregulated modulator of apoptosis (PUMA), to be markedly induced in the gastric mucosa of PHG patients [11]. Increased gastric mucosal apoptosis and decreased mucosal proliferation, were also noted in rats with PGH.

5. Factors influencing the development of portal hypertensive gastropathy

Many factors related to portal hypertension affect the presence and the severity of PHG. As the commonest cause of portal hypertension is liver cirrhosis, the presence or absence of cirrhosis, and its severity, may also affect the PHG.

5.1. Factors related to portal hypertension

- **Severity of portal hypertension:** The frequency of PHG is strongly correlated with the severity of portal hypertension, as indicated by hepatic venous pressure gradient (HVPG), esophageal intra-variceal pressure, and/or presence of esophageal varices and its size [12]. It was also found that portal hypertension associates with severe PHG, but not mild PHG,

this was evident in patients with severe PHG, which were discovered to have elevated HVPG, high hepatic sinusoidal resistance, and low hepatic blood flow, all markers of severe portal hypertension [12].

This leads us to the conclusion that not all patients with portal hypertension exhibit evidence of, or develop PHG. On the other hand, resolution of PHG, which occurs after intervention to decrease portal hypertension (by pharmacotherapy, trans-jugular intrahepatic portosystemic shunt (TIPS), or liver transplantation), may suggest an association between PHG and portal hypertension [13].

Thus, although PHG cannot be diagnosed without portal hypertension, it is however not the only factor that evokes PHG.

- **Correlation with varices**: Severe PHG is more common in patients with esophageal varices than patients without varices. It also, correlated positively with the size of varices; denoting, it was higher in those with large varices than in those with medium-sized or small varices [12].
- **Location of varices:** PHG was more commonly seen in patients with coexisting gastric and esophageal varices than in patients with only esophageal varices. Additionally, moderate or severe PHG was noted to be higher (not to a significant level) in patients with common collateral circulation *vs* uncommon collaterals. Portosystemic common collateral circulation includes esophageal varices, gastric varices, and vein dilatation (whether abdominal, umbilical, or hemorrhoid), while uncommon collaterals include splenorenal, gastric, renal, retroperitoneal, or cardiac angle venous shunts [14].
- **Portal vein diameter:** It was proposed that PHG is promoted by minimal collateral circulation since significant collaterals would otherwise reduce portal hypertension and gastric mucosal congestion. Later on, it was found that portal vein diameter in cirrhotic patients with PHG and no esophageal varices is greater than the portal vein diameter in patients with esophageal varices. This concept was further supported by the finding that patients with portal vein diameter < 12 mm have a significantly higher prevalence of esophageal varices than patients with larger portal vein diameter. It was then believed that the absence of reversed blood flow in the portal vein (due to the absence of hepatofugal flow), in patients without esophageal varices, meant that the pressure in the portal vein was not affected [15].
- **Esophageal variceal eradication:** PHG may appear for the first time in patients with portal hypertension, or increase in severity in patients with pre-exciting PHG after eradication of esophageal varices by either endoscopic variceal ligation or endoscopic variceal sclerotherapy [16], thus patients with well developed fundal varices are more liable to develop PHG after obliteration of the varices than patients with poorly developed fundal varices. Since fundal varices are usually formed by a gastro-renal shunt, this finding supports the view that the presence of a gastro-renal shunt may play a protective role in the development of PHG after variceal obliteration. Therefore; some patients may exhibit minimum or no change in PHG after esophageal eradication [17].

Other techniques are also used for obliteration of the esophageal varices including angiographic variceal obliteration (which increases the PHG frequency), and percutaneous transhepatic variceal embolization; after which 38% of the patients develop *De-novo* PHG. The development of PHG for the first time or its increase in frequency and/or its severity is attributed to increased gastric mucosal congestion due to a decrease in the blood flow in the esophageal varices, which leads to an increase in the portal blood flow.

This phenomenon can be explained by obliteration of the blood flow after eradication of esophageal varices, this can lead to increased portal pressure and redistribution of residual blood flow that had passed through the previously patent varices. This mechanism is supported by the finding that gastric mucosal blood flow increases after variceal ligation [4].

Some investigators believe that the higher rate of PHG in patients undergoing endoscopic variceal eradication (sclerotherapy or banding) merely reflects other factors rather than the procedures *per se*, factors like; increased duration of portal hypertension, advanced liver disease, or severe portal hypertension in patients selected to undergo variceal eradication, must be evaluated in patients who developed PHG or showed an increase in its severity [18]. Nevertheless, higher frequency of PHG in patients undergoing sclerotherapy, suggest that portal hypertension is still the main underlying cause of PHG

5.2. Factors related to liver cirrhosis

- **Cirrhotic vs non-cirrhotic portal hypertension:** Primary liver disease usually occurs in PHG, but is not essential for PHG, provided another cause of portal hypertension exists. Consequently, PHG can occur in patients with other causes of portal hypertension; non-cirrhotic portal fibrosis, pre-hepatic or post-hepatic portal hypertension [19].

  Portal pressure is not the only factor that is determinant of PHG, other factors, like cirrhosis, may be implicated in the development of the mucosal lesions, which are characteristic of PHG. PHG was found to occur more commonly in patients with cirrhotic liver than in non-cirrhotic portal hypertension patients, also the patients with cirrhosis have a more aggressive course of PHG with faster progression to more severe PHG as time advances [19].

Taking this in consideration, other factors may also be involved in the pathogenesis of PHG. For example, in patients with portal hypertension and cirrhosis, there is an increase in the level of many vasodilator substances in systemic circulation e.g. gastrin, secretin, and VIP, this increase in the level of vasodilator or the decrease in the sensitivity to vasoconstrictor substance may have a role in the underlying mechanism of PHG [10]. However, these changes were also found in cirrhotic patients not suffering from PHG, thus the exact picture of the pathogenesis is not yet fully understood.

- **Duration of liver disease:** The duration of liver disease positively correlates with development of PHG, with average cumulative incidence of 3% at 1 year, 10% at 2 years, and 24% at 3 years [7].
- **Liver disease severity:** PHG is correlated with liver disease severity, as measured by Child-Turcotte-Pugh score (CTP score) (**Table 2**), Child-Pugh stage C cirrhosis is associated with more frequent and faster progression of PHG. Also, it was found that cirrhotic patients

with severe PHG (especially those without esophageal varices) had more frequent CTP stage C than patients with mild PHG [7].

Model for end-stage liver disease (MELD) is another important scoring system for assessing liver disease severity, which was found to significantly correlate with PHG severity [20].

On the other hand, the severity of PHG was correlated to markers of advanced liver disease (like hypoalbuminemia and hyperbilirubinemia) which are biochemical markers of advanced liver disease. Markers of portal hypertension (thrombocytopenia) and of insulin resistance (hyperglycemia), were also significant independent predictors of PHG [21].

5.3. Other factors

Many other factors may be involved in the pathogenesis of PHG, this includes thrombocytopenia or splenomegaly which are associated with the severity of PHG. Additional factors like an increase in the thickness of the lesser omentum and the presence of a splenorenal shunt were found to correlate with PHG in patients with chronic liver disease [22].

5.3.1. Factors that do not affect the risk of PHG

Although, portal hypertension is essential for PHG diagnosis, there is still no association between the etiology of portal hypertension and PHG. Similarly, as cirrhosis is the common cause of portal hypertension, there is no correlation between the underlying causes of cirrhosis and PHG. Moreover, in cirrhotic patients, the role of Helicobacter pylori (H. pylori) in the pathogenesis of PHG is not fully understood. Some contributed that Helicobacter has no role in the pathogenesis of PHG in these patients [23]. However, there is evidence of association between H. pylori infection and PHG in cirrhotic patients, in these patients, Helicobacter infection may be related to the severity of PHG. This was strengthened by the fact that there was mild improvement of PHG after H. pylori eradication. Therefore, we can conclude that there may be a minor role for H. pylori in the pathogenesis of PHG in cirrhotic patients [23]. Further studies on large number of patients are conducted to show the effect of H. pylori eradication in the treatment of PHG, especially severe portal gastropathy in cirrhosis.

Parameter	**Point assigned**		
	1	**2**	**3**
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dl)	<2	2–3	>3
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Slight-moderate	Tense
Encephalopathy	0	1–2	3–4

A total Child-Turcotte-Pugh score of 5–6 considered class A, 7–9 is class B, and 10– 15 is class C. INR, international normalized ratio.

Table 2. Child-Turcotte-Pugh score.

Also, there is no evidence that there is any increase in the prevalence or severity of PHG with the use of either nonsteroidal anti-inflammatory drugs (NSAIDs), or COX-(cyclooxygenase)-2 inhibitor [24]. Another negative correlation was found between alcohol and smoking alongside PHG, thus there is no benefit from abstinence or quitting smoking [25]. Likewise, the presence of PHG was independent of patient's age, or sex.

6. Whom should go for screening for PHG

Patients with portal hypertension and chronic iron deficiency anemia who are suspected to have chronic bleeding should go for PHG screening. Chronic bleeding is diagnosed when there is either decrease in hemoglobin level below 2 g/dL within 6-month, or if there is presence of iron deficiency anemia with a positive fecal occult blood test. For those patients, upper endoscopy can confirm the diagnosis of PHG [26].

7. Natural history

PHG may change in an individual patient over time, about 30% of the patients with cirrhosis and mild PHG, progress to severe PHG during a 10 year follow up period, considering that these patients did not receive any prophylactic treatment. Most of the patients with worsening PHG, severe lesions, or *de novo* PHG develop bleeding. There are only a few improved cases in PHG without treatment [27]. Furthermore, Patients who have PHG associated with cirrhosis-related portal hypertension have more frequently persistent and progressive PHG, which is more likely to bleed than patients with PHG related to non-cirrhotic portal hypertension [9].

Although, as mentioned above, patients with previous endoscopic therapy (sclerotherapy or endoscopic variceal ligation) have a higher prevalence of PHG, the clinical course of PHG in this context, particularly in non cirrhotic portal hypertension, may be milder and transient [28].

PHG is a dynamic condition emphasized by the observation that 30% of patients who have endoscopic features of PHG remained unchanged throughout follow-up period, whereas 25% of patients show either worsening or improvement of the condition during the follow up period. Thus, not only can PHG appear for the first time or progress from mild to severe condition over time, but it can also revert from severe to mild, and even disappear completely with treatment [23].

8. Clinical picture

Most patients with PHG are asymptomatic, but a significant number of patients exhibit symptoms related to iron deficiency anemia from chronic GI bleeding. Bleeding from PHG may be either chronic occult blood in the stool, or overt which occurs in a smaller proportion of patients. Endoscopic diagnosis of acute hemorrhage from PHG is established when there is active bleeding from gastropathy lesions, if non-removable clots overlying these lesions is

observed, or when there is PHG and no other cause of acute bleeding can be demonstrated after thorough evaluation of the gastrointestinal tract [9]. Recurrent bleeding is common in PHG after the initial episode.

Although all PHG patients with chronic bleeding develop severe chronic iron deficiency anemia, no study has evaluated the prevalence of PHG in cirrhotic patients with chronic iron deficiency anemia. In patients with portal hypertension, with or without cirrhosis and chronic iron deficiency anemia, chronic bleeding from PHG must be suspected, its diagnosis is confirmed by upper endoscopy. Comprehensive study of the whole gastrointestinal tract in these patients by capsule endoscopy is mandatory to exclude similar lesion elsewhere along gastrointestinal tract e.g. colonopathy [27].

8.1. Diagnosis

The diagnosis of PHG is done mainly by upper endoscopy. The endoscopic findings of PHG diagnosis was classified by the New Italian Endoscopic Club according to its severity based on the presence of four elementary lesions: mosaic like pattern, red point lesions, cherry red spots, and black brown spots (**Figure 1**) [29]. Early change in PHG is called scarletina, which appears as a fine pink speckling. On the other side, severe PHG appear as cherry red spots that may become confluent and is very friable, so it can actively bleed during endoscopy. These lesions are present predominantly in the fundus and/or the corpus of the stomach, yet PHG–like lesions have been described in other sites in the gastrointestinal tract e.g. the rectum, colon, and small bowel in asymptomatic patients and in patients with bleeding [29].

8.2. Endoscopic evaluation of PHG

The elementary lesions of PHG according to the New Italian Endoscopic Club for the Study and Therapy of Esophageal Varices [NIEC] classification are as follows [30]:

(1) Mosaic-like pattern (MLP); it is described as the presence of small, polygonal areas in the center (areola) surrounded by a whitish-yellow depressed border. The term mosaic is further subdivided according to the color of the areola into; mild, when the areola is uniformly pink, moderate, if the center is red, and severe, when the areola is uniformly red.

(2) Red-point lesions (RPLs) are defined as red, small, flat lesions, and <1 mm in size.

(3) Cherry-red spots (CRSs) are defined as red, round lesions, >2 mm in diameter, which slightly protrude into the lumen of the stomach.

(4) Black-brown spots (BBSs) are defined as irregularly flat spots, either black or brown in color, does not disappear after washing, and it is due to intra-mucosal hemorrhage.

PHG is classified by endoscopy, into mild, moderate and severe forms. PHG mucosa can be seen as snakeskin (MLP) in mild cases, while RPLs, CRSs or BBCs that is liable to bleeding, are found in severe cases, however, the presence of red or brown spots without bleeding is considered a moderate disease [35].

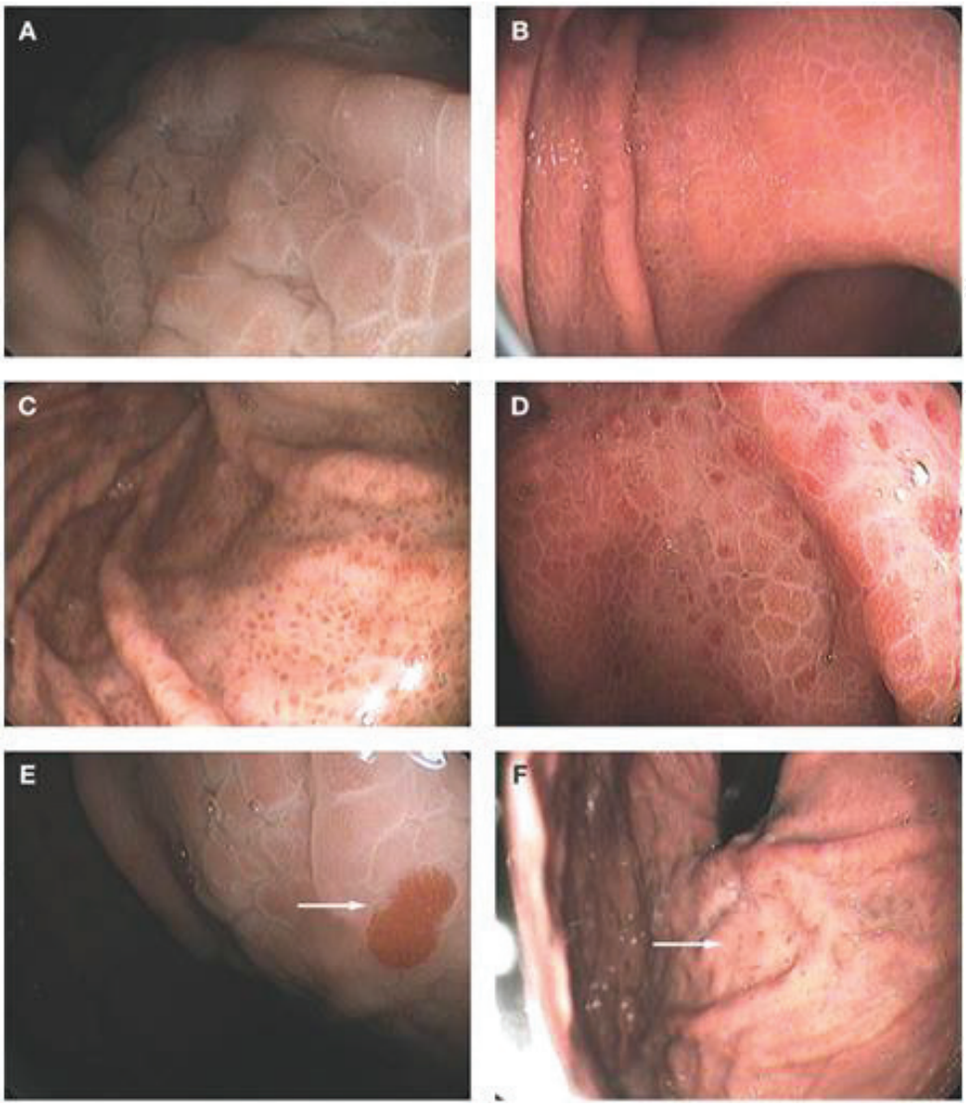

Figure 1. Endoscopic images of portal hypertensive gastropathy that show the four main findings of this condition. Mild (A) and moderate (B) mosaic-like gastric mucosal pattern, red point lesions (C), cherry-red spots (D), and black–brown spots, including an intramucosal hemorrhage (E) and a brown spot (F).

8.3. Classification of portal hypertensive gastropathy

PHG is classified on the basis of the condition's severity, therefore many classifications of the PHG mucosa have been proposed. McCormack's classification, NIEC's and Tanoue's classifications are the most popular used classifications (**Table 3**). McCormack classified the mucosal changes into two main categories, mild and severe, on the other hand, the NIEC classification has three categories; mild, moderate and severe, and further subdivided the mosaic-like pattern into three groups [28]. Finally, the McCormack classification, a two-category classification system, is the recommended one. The classification comprises of:

Mild portal hypertensive gastropathy: Only one change in the stomach mucosa is present, that of appearance of mosaic or snakeskin pattern on it.

	McCormack	NIEC	Tanoue
Mild	Scarlatina type rash		
	Snake skin	Pink in center mosaic	Mild redness
	Striped appearance		
Moderate	–	Flat red spots mosaic	Fine red speckling mosaic
Severe	Red spots	Diffusely red mosaic	Point bleeding
	Diffuse hemorrhagic lesions		

Table 3. Endoscopic finding and classification of PHG.

Severe portal hypertensive gastropathy: In addition to the mosaic or snakeskin pattern of the stomach mucosa; bulging, flat red or black-brown spots are seen. There also may be active bleeding.

In the rare instance where PHG cannot be clearly diagnosed on the basis of endoscopic appearance and location alone, biopsy for histology may prove useful [28].

8.4. Histologically

The unique histological features of PHG are marked dilatation of the capillaries and collecting venules in the gastric mucosa with markedly congested and tortuous submucosal venules (**Figure 2**) [31]. These vascular features are present in the absence of any inflammatory cell

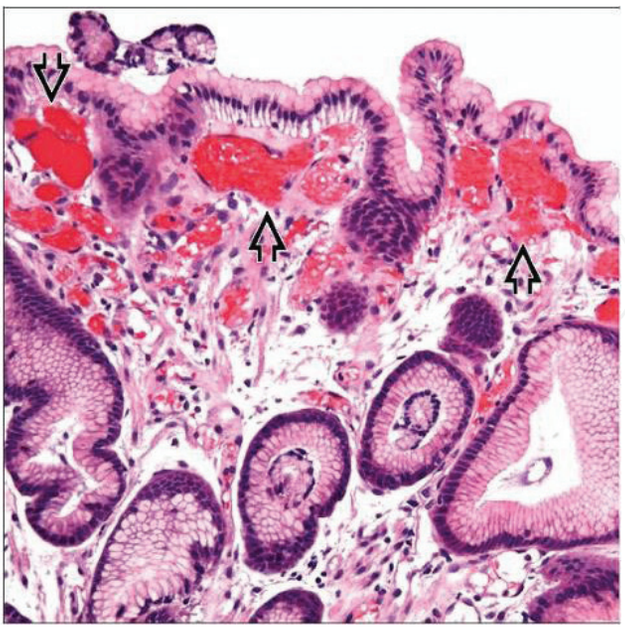

Figure 2. Hematoxylin and eosin shows numerous dilated capillaries in the superfacial gastric mucosa. These are not entirely specific for PHG.

infiltrate or erosion of the gastric mucosa. Stromal fibrosis and edema of the lamina propria can also be seen [31].

It may be difficult to differentiate between severe PHG and gastric antral vascular ectasia (GAVE) by endoscopic examination, so biopsy is beneficial in this case, as GAVE has distinct histological features that can set it apart from severe PHG. GAVE has many fibrin thrombi in the mucosal vessels with ectasia and spindle cell proliferation (smooth muscle and myofibroblast hyperplasia) in the superficial mucosa. Furthermore, fibrohyalinosis is more commonly present in GAVE. All of these findings provide additional features that help in differentiating between severe PHG and GAVE [32].

8.5. Portal gastropathy score calculation

Table 4 shows the scoring system to calculate the severity of PHG, the calculation depends on three categories: *Microscopic picture*; score 1 considered for mild findings, and score 2 for severe findings. *Red marks*; isolated lesion is considered score 1, whereas confluent red marks is scored 2. *GAVE*; if absent scored 0, while its presence is scored 2. If the total score was equal to 3 or less, the PHG is mild, on the other hand if the score is 4 or greater, PHG is severe [33].

8.6. Other diagnostic modalities

8.6.1. Non-endoscopic methods for diagnosis of HPG

Other non-endoscopic methods for the diagnosis of PHG such as MRI and CT are not yet considered as routine investigation for the diagnosis of PHG. Their results must be further evaluated to warrant their role in the diagnosis of PHG. Endoscopy still remains the main diagnostic method [34].

In CT scan, enhancement of the inner layer of the gastric walls due to gastric congestion, characterizes PHG lesion. Similarly, MRI is used to measure the diameter of collateral veins e.g. the left gastric, paraesophageal, and azygos veins to confirm the diagnosis of portal hypertension. In patients with PHG, the measurement of the diameters of these veins does not differ from those

Endoscopic findings	Parameter	Score
Mucosal mosaic pattern	Mild	1
	Severe	2
Red markings	Isolated	1
	Confluent	2
Gastric antral vascular ectasia (GAVE)	Absence	1
	Presence	2

Mild portal hypertensive gastropathy ≤ 3; severe portal hypertensive gastropathy ≥ 4.

Table 4. Portal hypertensive Gastropathy scoring system.

in patients without PHG, therefore it is not helpful in the diagnosis. These data suggest that these imaging techniques is still in its infancy period and best reserved for experimental purposes [35].

8.7. Differential diagnosis

The endoscopic findings of the gastric mucosa include many differential diagnoses of several disorders. When red spots are seen in the stomach by endoscopy, important diagnostic considerations are evoked. GAVE or watermelon stomach which is a common differential diagnosis of PHG, has characteristic endoscopic findings which are linear red stripes, separated by normal mucosa, these findings give the appearance of a watermelon, that is seen in the gastric antrum or proximal stomach. GAVE and PHG are distinct entities, however both are encountered in cirrhotic patients. While PHG routinely affects the gastric body and fundus, GAVE almost exclusively inhabits the antrum [32].

These findings have a diagnostic accuracy of 85% for GAVE and help distinguish it from PHG.

Table 5 further shows the differences between GAVE and PHG, however, there may be an overlap between GAVE and PHG in cirrhosis with portal hypertension [6].

Other conditions that increase the dilemma of PHG diagnosis include simple acute gastritis caused by non-steroidal anti–inflammatory drug (NSAIDS) or *H. pylori*, which may have a mosaic like pattern endoscopically but, the main histopathological feature in gastritis is inflammatory cell infiltration with minor vascular dilation, and it is also localized to the mucosa (superficial lesion). Lastly, endoscopic lesions similar to PHG may be also seen in some uncommon diseases e.g. polycythemia, gastric purpura, and Osler-Weber-Rendu disease [36].

	PHG	**GAVE**
Underlying etiology	Portal hypertension with or without cirrhosis	Can be present without portal hypertension, such as chronic renal failure, connective tissue disorders, and bone marrow transplantation
Predominant location	Fundus and corpus	Antrum
Endoscopic appearance	Mosaic like pattern or red marks	Linear red strips separated by normal mucosa
Pathological findings	Dilatation of the capillaries, and collecting venules in the gastric mucosa. Ectasia of submucosal veins, with intimal thickening	Fibrin microthrombi, myofibroplast hyperplasia, fibrinolysis
Management		
• **Response to beta blockers**	Yes	No
• **TIPS**	Yes	No
• **Endoscopic therapy ACP**	Used in refractory bleeding	Preferable as first line

ACP, argon plasma coagulation.

Table 5. Comparison between portal hypertensive gastropathy and gastric antral vascular ectasia.

9. Management of PHG

The goal of management of PHG is to reduce portal pressure.

9.1. Primary prophylaxis

PHG in asymptomatic patients who have no evidence of bleeding is discovered accidentally during screening for either chronic iron deficiency anemia or for esophageal varices in patients with cirrhosis. Till now, there is no recommendation to start any primary prophylaxis to prevent bleeding from PHG patients, except if there is an indication of beta-blocker for other reasons. However, in asymptomatic patients with both esophageal varices and PHG, if the patient undergoes esophageal eradication therapy, co-administration of a nonselective beta-blocker is beneficial. The dose of beta blocker should be titrated to a goal heart rate of 55–60 bpm or a 25% reduction from baseline. On the other hand, in patients with severe PHG and no varices, starting prophylaxis therapy with nonselective beta-blockers, should be considered. Yet, this approach is controversial, and more research is needed to clarify the prophylactic role of beta-blockers as primary prophylaxis for bleeding from PHG [34].

9.2. Secondary prophylaxis

Beta-blockers (like propranolol or nadolol) are used as secondary prophylaxis, and are the basis of therapy, to prevent recurrent bleeding from PHG. It is not only used to prevent the bleeding, but it also improves the severity score of PHG by endoscopy, changing it from severe to mild, or even completely curing it. On the other hand, about 50% of PHG patients especially cirrhotic during a 2-year follow up, show mild or even no response to beta blocker therapy. For those patients adding isosorbide 5-mononitrate may have a synergistic effect to reduce the portal pressure [37].

Addition of beta-blocker therapy to endoscopic management of varices is beneficial in reducing the progression of PHG after endoscopic therapy of varices. Propranolol, a non-selective beta-blocker (24–480 mg/day), has been commonly used in these cases. The dose of propranolol should be increased gradually to maximum dose (up to 160 mg twice daily) with targeted heart rate of 55–60 bpm, and should be continued as long as there is portal hypertension [37]. In patients with iron deficiency anemia, iron replacement therapy and beta blocker should be started simultaneously.

9.3. Treatment of chronic bleeding

Patients with PHG with or without cirrhosis, and chronic blood loss are commonly presented with iron deficiency anemia. Thorough investigation of these patients must be done to rule out other causes of iron deficiency anemia before attributing PHG as the cause. All patients with PHG and iron deficiency anemia should start iron-replacement therapy either; oral preparations, or intravenous (IV) iron.

To reduce chronic bleeding from PHG, with or without portal hypertension, portal pressure should be reduced, therefore non selective beta blocker is the first line of treatment. The use of beta blockers has proved efficient, based on both experimental and clinical investigations

demonstrating that, propranolol reduces portal pressure and cause vasoconstriction in the overall splanchnic vascular bed.

Anti-oxidants have also been used to treat PHG. Experimentally, Vitamin E led to complete reversal of susceptibility of PHG mucosa to alcohol injury, in rats. Vitamin E also, led to the restoration of normal Extracellular signal-regulated kinase (ERK-2 signaling), which plays a pivotal role in healing after gastric mucosal injury. Thus, vitamin E may have a protective effect on the PHG mucosa [38].

Use of other pharmacological agents such as losartan, thalidomide and corticosteroids have been prescribed in the treatment of chronic bleeding from PHG. However, the evidence supporting their use in PHG bleeding is weak [39].

9.4. Treatment of acute bleeding

- For acute bleeding; initial stabilization with octreotide or terlipressin to stop the bleeding, followed by initiation of beta-blockers as secondary prevention is recommended. During acute bleeding from PHG, the patients may be hemodynamically unstable, therefore beta blocker therapy must be reserved, regarding its drawback, as it has a negative effect on heart and the circulation. Despite the drawbacks of beta-blocker therapy, it is considered immediately after the patient becomes hemodynamically stable, usually within 3 days. This highlights their important role in the management of acute as well as chronic GI bleeding.
- Octreotide, a somatostatin analogue (100 μg bolus followed by an infusion of 25 μg/h for 48 h), and Terlipressin, a vasopressin analogue, are both effective in the treatment of acute bleeding caused by PHG. Vasopressin and omeprazole when used together are more effective in controlling the acute bleeding than when vasopressin is used alone [40].

9.5. For refractory cases

When the patients do not respond to the previously mentioned treatments, invasive intervention must be done. Transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt are considered as salvage therapy only when they are performed in certain circumstances and in an expert center due to their significant morbidity and mortality results [41].

Surgical shunting has also proved beneficial in refractory bleeding from PHG however, this benefit is limited by an increase in the risk of deterioration of the hepatic function in patients with cirrhosis. Only cirrhotic patients with Child Pugh score A or B found improved outcomes from surgical shunting with reduced mortality. Comparing the results of TIPS with surgical shunt, it is reported that surgical shunt reduced re-bleeding, with fewer shunt complication e.g. shunt revisions, stent thrombosis, re-stenosis, and re-intervention of TIPS. However, long-term mortality was similar. On the other hand, similar results were found between TIPSS and distal splenorenal shunting with regards to re-bleeding, encephalopathy, and survival. Whatever the method of shunting in case of refractory bleeding from PHG, it should always be performed in expertise center. Surgical shunting may be an option only in CTP stage A cirrhosis with PHG or in patients with non-cirrhotic portal hypertension [42].

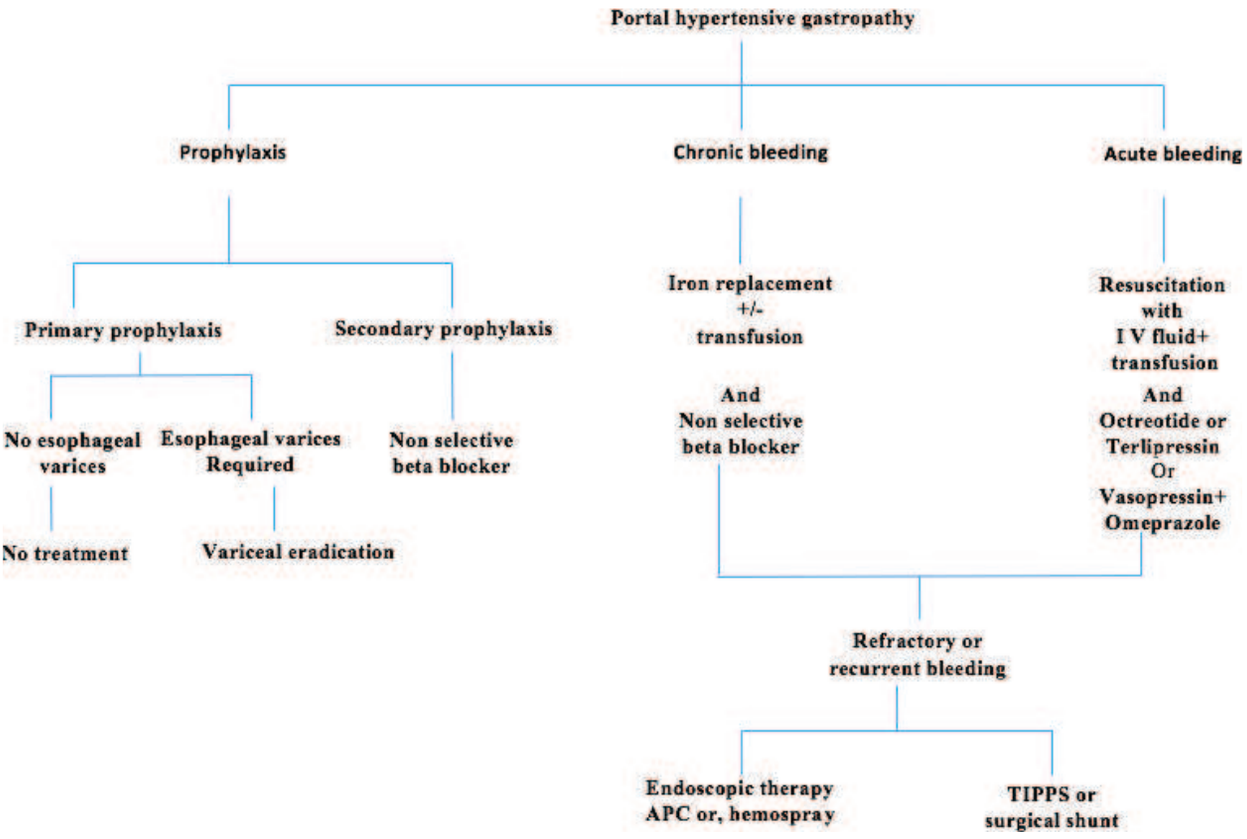

Figure 3. Treatment algorithm of portal hypertensive gastropathy.

Argon plasma coagulation (APC) is an electrosurgical technique used for treatment of bleeding of PHG. APC is a noncontact thermal coagulation, high frequency current, that is applied to the bleeding site through an argon plasma jet, this creates effective hemostasis and a homogenous surface coagulation with limited depth penetration. Treatment with APC decrease the need of transformation and improve the hemoglobin level in PHG patients, accordingly APC is an effective and rapid therapy to control bleeding from PHG, especially if there is a contraindication for beta blockers. If beta blocker can be used, co administration with APC has a synergistic effect in controlling PHG bleeding [5].

Hemospray: In patients with acute active bleeding due to PHG, it may be useful to use hemostatic powder that acts as a barrier to enhance the action of the clotting factors, giving time for the coagulation process to act and stop the bleeding [43]. A treatment algorithm for patients with PHG is described in **Figure 3**.

10. Mortality rates

Limited data on mortality due to bleeding from PHG is available, but the bleeding from PHG is rarely fatal. It represents a small percentage if compared with the mortality from other causes of gastrointestinal bleeding due to portal hypertension, and especially in comparison

to variceal bleeding. Also, in cirrhotic patients it represents only <1% of the mortality, because the bleeding is typically mild [4]. As bleeding from PHG is an unusual direct cause of death, it does not affect the survival in cirrhotic patients. However, anemia from chronic bleeding or repeated acute bleeding may lead to deterioration of the liver function.

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