

Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy

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Author contributions: Gjeorgjievski M and Cappell MS are equal authors; they contributed equally to conceiving and planning this project, to performing the systematic review, to retrieving and analyzing the data from the literature, to writing the manuscript, and to editing of the final manuscript.

Conflict-of-interest statement: None for all authors. This paper does not discuss any confidential pharmaceutical industry data reviewed by Cappell MS as a consultant for the United States Food and Drug Administration (FDA) Advisory Committee on Gastrointestinal Drugs. Cappell MS is a member of the speaker's bureau for AstraZeneca. This paper does not discuss any drug manufactured or marketed by AstraZeneca.

Data sharing statement: The paper has no original data or original statistics presented. No additional data are, therefore, available.

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Received: October 2, 2015
Peer-review started: October 4, 2015

First decision: November 4, 2015

Revised: November 30, 2015

Accepted: January 16, 2016

Article in press: January 19, 2016

Published online: February 8, 2016

Abstract

AIM: To describe the pathophysiology, clinical presentation, natural history, and therapy of portal hypertensive gastropathy (PHG) based on a systematic literature review.

METHODS: Computerized search of the literature was performed *via* PubMed using the following medical subject headings or keywords: "portal" and "gastropathy"; or "portal" and "hypertensive"; or "congestive" and "gastropathy"; or "congestive" and "gastroenteropathy". The following criteria were applied for study inclusion: Publication in peer-reviewed journals, and publication since 1980. Articles were independently evaluated by each author and selected for inclusion by consensus after discussion based on the following criteria: Well-designed, prospective trials; recent studies; large study populations; and study emphasis on PHG.

RESULTS: PHG is diagnosed by characteristic endoscopic findings of small polygonal areas of variable erythema surrounded by a pale, reticular border in a mosaic pattern in the gastric fundus/body in a patient with cirrhotic or non-cirrhotic portal hypertension. Histologic findings include capillary and venule dilatation, congestion, and tortuosity, without vascular fibrin thrombi or inflammatory cells in gastric submucosa. PHG is differentiated from gastric antral vascular ectasia by a different endoscopic appearance. The etiology of PHG is inadequately understood. Portal hypertension is necessary but insufficient to develop PHG because many patients have portal hypertension without PHG.

PHG increases in frequency with more severe portal hypertension, advanced liver disease, longer liver disease duration, presence of esophageal varices, and endoscopic variceal obliteration. PHG pathogenesis is related to a hyperdynamic circulation, induced by portal hypertension, characterized by increased intrahepatic resistance to flow, increased splanchnic flow, increased total gastric flow, and most likely decreased gastric mucosal flow. Gastric mucosa in PHG shows increased susceptibility to gastrotoxic chemicals and poor wound healing. Nitrous oxide, free radicals, tumor necrosis factor- α , and glucagon may contribute to PHG development. Acute and chronic gastrointestinal bleeding are the only clinical complications. Bleeding is typically mild-to-moderate. Endoscopic therapy is rarely useful because the bleeding is typically diffuse. Acute bleeding is primarily treated with octreotide, often with concomitant proton pump inhibitor therapy, or secondarily treated with vasopressin or terlipressin. Nonselective β -adrenergic receptor antagonists, particularly propranolol, are used to prevent bleeding after an acute episode or for chronic bleeding. Iron deficiency anemia from chronic bleeding may require iron replacement therapy. Transjugular-intrahepatic-portosystemic-shunt and liver transplantation are highly successful ultimate therapies because they reduce the underlying portal hypertension.

CONCLUSION: PHG is important to recognize in patients with cirrhotic or non-cirrhotic portal hypertension because it can cause acute or chronic GI bleeding that often requires pharmacologic therapy.

Key words: Portal hypertensive gastropathy; Congestive gastropathy; Portal hypertension; Cirrhosis; Cirrhotic; Chronic liver disease; Nonvariceal upper gastrointestinal bleeding; Esophageal varices; Hepatic fibrosis

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Core tip: Portal hypertensive gastropathy (PHG) is diagnosed by characteristic endoscopic findings of variably erythematous, small, polygonal areas surrounded by a whitish, reticular border in a mosaic pattern in the gastric fundus/body in a patient with portal hypertension of any etiology. The pathophysiology of PHG is inadequately understood. Portal hypertension is a prerequisite to develop PHG. PHG increases in frequency with increasing portal hypertension, liver disease progression, duration of liver disease, presence of esophageal varices, and endoscopic variceal obliteration. Pathogenesis is related to a hyperdynamic circulation induced by portal hypertension. Gastric mucosa in PHG exhibits greater susceptibility to gastrotoxic chemicals and poor wound healing. Acute or chronic gastrointestinal bleeding are the only clinical complications. Bleeding is typically mild-to-moderate and rarely fatal. Endoscopic therapy is rarely useful. Pharmacotherapy for acute bleeding includes octreotide with concomitant proton-pump-inhibitor therapy, or alternatively vasopressin. Nonselective β -adrenergic receptor antagonists, particularly propranolol, are used

to prevent re-bleeding after acute bleeding or for chronic bleeding. Transjugular-intrahepatic-portosystemic-shunt and liver transplantation is ultimate therapies because they treat the underlying portal hypertension.

Gjeorgjievski M, Cappell MS. Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy. *World J Hepatol* 2016; 8(4): 231-262 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i4/231.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i4.231>

INTRODUCTION

Portal hypertensive gastropathy (PHG) is an important, but underappreciated, cause of morbidity in patients with cirrhotic or non-cirrhotic portal hypertension. Researchers have recently intensely focused on this inadequately understood disease. However, the research studies have been published in a wide spectrum of journals including basic or biomedical journals not readily accessible to clinicians and a review incorporating the recent basic and clinical advances in this rapidly evolving subject is needed. This work systematically reviews this entity including pathophysiology, clinical presentation, natural history, and established, evolving, or experimental therapy, with a focus on data relevant to clinicians and an emphasis on recent data. This work aims to describe what is known about the disease and to expose gaps, requiring further research, in our current understanding of this disease.

MATERIALS AND METHODS

Computerized search of the literature was performed *via* PubMed using the following medical subject headings or keywords: "portal" and "gastropathy"; or "portal" and "hypertensive"; or "congestive" and "gastropathy"; or "congestive" and "gastroenteropathy". The following criteria were applied for study inclusion: Publication in peer-reviewed journals, and publication since 1980, except for publications from 1957-1980 of historical significance reviewed in the history section. Articles were independently evaluated by each author and selected for inclusion by consensus after a thorough discussion based on the following criteria: Well-designed, prospective trials; recent studies; large study populations; and study emphasis on PHG. However, data from retrospective series, reviews from internationally recognized authorities, and even case reports were included when prospective trials were unavailable.

RESULTS

History

Palmer^[1], in 1957, proposed that the pathogenesis of erosive gastritis in cirrhotic patients was different than that in non-cirrhotic patients and that erosive gastritis

Table 1 Rates of portal hypertensive gastropathy in patients with portal hypertension

Ref.	Analyzed patients	Total number	No. (%) with PHG	No. (%) with mild PHG	No. (%) with severe PHG
McCormack <i>et al</i> ^[3]	Portal hypertension	127	65 (51%)	37 (29%)	28 (22%)
Sarin <i>et al</i> ^[5]	Portal hypertension	136	10 (7%)		
DeWeert <i>et al</i> ^[6]	Non-alcoholic liver disease	81	23 (28%)	Not reported	Not reported
McCormick <i>et al</i> ^[7]	Portal hypertension	93 endoscopies in 74 patients	85 endoscopies (91%)	6 (6%), moderate 61 (66%)	18 (19%)
Sarin <i>et al</i> ^[8]	Portal hypertension	107	4 (3.7%) (only cirrhotic)	Not reported	Not reported
Parikh <i>et al</i> ^[9]	Portal hypertension	118	71 (60%)	41 (58%)	30 (42%)
Sarin <i>et al</i> ^[10]	Portal hypertension with prior variceal bleeding	967	86 (9%)	56 (5.8%)	30 (3.1%)
Itha <i>et al</i> ^[11]	EHPVO in children	163	(12%)	Not reported	Not reported
Rana <i>et al</i> ^[12]	Portal hypertension	41	27 (66%)	19 (46%)	8 (20%)
El-Rifai <i>et al</i> ^[13]	Portal hypertension	24	14 (58%)	10 (42%) - moderate	4 (16%)
Sogaard <i>et al</i> ^[14]	Portal vein thrombosis	67	28 (42%)	Not reported	Not reported
Figueiredo <i>et al</i> ^[15]	Portal hypertension; cirrhosis	36	27 (75%)		5 (46%)
Erden <i>et al</i> ^[16]	Portal hypertension	57	15 (26.3%)	Not reported	Not reported
Duché <i>et al</i> ^[17]	Children, portal hypertension with biliary atresia	125	27 (21%)	Not reported	Not reported
Aydođan <i>et al</i> ^[18]	Portal hypertension	51	30 (58%)	Not reported	Not reported
dos Santos <i>et al</i> ^[19]	Portal hypertension	43	22 (51%)	Not reported	Not reported
Pantham <i>et al</i> ^[20]	Esophageal varices undergoing TEE	24	12 (50%)	Not reported	Not reported
Abdollahi <i>et al</i> ^[21]	Autoimmune hepatitis	60	27 (45%)	Not reported	Not reported
de Alcantara <i>et al</i> ^[22]	Chronic liver disease vs EHPVO	35 vs 18	7 (20%) vs 8 (44.4%)	Not reported	Not reported
Aoyama <i>et al</i> ^[23]	Portal hypertension	119	35 (29%)	Not reported	Not reported

PHG: Portal hypertensive gastropathy; EHPVO: Extrahepatic portal vein obstruction; TEE: Transesophageal echocardiogram.

in cirrhotic patients resulted from mechanical venous back-pressure from portal hypertension, rather than a circulating, mucosal, or intraluminal toxic factor. This proposal was supported by successful reversal of erosive gastritis in cirrhotic patients with portal decompression by surgical shunts^[1]. In 1984, Sarfeh *et al*^[2] recognized a distinct form of gastric mucosal hemorrhage in patients who had portal hypertension, demonstrated by cirrhosis and gastroesophageal varices, which they called "portal hypertensive gastritis". They proposed that gastric mucosa in portal hypertension reacts differently from gastric mucosa without portal hypertension and these patients with portal hypertension may benefit from portal decompressive surgery. One year later, McCormack *et al*^[3] reported that the gastritis in patients with portal hypertension differed from that in patients without portal hypertension in mucosal histology, nonresponse to standard therapy for conventional gastritis, and in occasionally having very similar histological changes in other gastrointestinal (GI) organs such as the colon. They called these gastritis-like changes in patients with portal hypertension "congestive gastropathy"^[3], and classified it as "mild" or "severe", using criteria described by Taor *et al*^[4].

Epidemiology

PHG can present at any age, including pediatric or adult patients. The reported prevalence of PHG varies greatly from 20% to 75% in patients with portal hypertension (Table 1)^[3,5-23], and varies greatly from about 35% to 80% in patients with cirrhosis (Table 2)^[21,23-68]. For

example, in a study of 373 cirrhotic patients, 299 (80.2%) had PHG^[34]. In the HALT-C trial, 374 (37%) of 1011 patients with biopsy-proven cirrhosis or bridging fibrosis from hepatitis C had PHG^[69]. This wide variability likely reflects variability in classification criteria, interpretation of endoscopic lesions, study populations, and natural history of PHG^[10,70,71].

PHG is usually mild as reported by McCormack *et al*^[3] or in the NIEC study^[32,70]. The prevalence of mild PHG in patients with portal hypertension ranges from 29%-57%, and of severe PHG ranges from 9%-46%^[71].

Risk factors for PHG

The main predictors of PHG are portal hypertension and severe liver disease^[72].

Portal hypertension: Most studies show that the frequency and severity of PHG is strongly correlated with the severity of portal hypertension, as indicated by multiple parameters, including hepatic venous pressure gradient (HVPG)^[36,57], esophageal intravariceal pressure^[29], and presence or size of esophageal varices^[34,42,57,62,73]. Merkel *et al*^[36] reported that the severity of PHG was correlated with the severity of portal hypertension as determined by HVPG, but this correlation was significant only for severe PHG (HVPG = 20.5 ± 4.0 mmHg) vs no PHG (HVPG = 17.4 ± 5.2 mmHg, *P* = 0.0004), and not for mild PHG (HVPG = 16.1 ± 3.2 mmHg) vs no PHG [17.4 ± 5.2 mmHg, not significant (NS)]. In a prospective study of 331 cirrhotic patients, Kim *et al*^[57] found that patients with severe

Table 2 Rates of portal hypertensive gastropathy in patients with cirrhosis

Ref.	Patients	Total number	PHG	Mild	Severe
Sacchetti <i>et al</i> ^[24]	Cirrhosis	142	38 (27%)	28 (20%)	10 (7%)
D'Amico <i>et al</i> ^[25]	Cirrhosis	212	130 (61%)	110 (52%)	20 (9%)
Calès <i>et al</i> ^[26]	Cirrhosis	100	98 (98%)	57 (57%)	41 (41%)
Rabinovitz <i>et al</i> ^[27]	Cirrhosis	510	(43%)	Not reported	Not reported
Iwao <i>et al</i> ^[28]	Cirrhosis	47	32 (68%)	15 (32%)	17 (36%)
Taranto <i>et al</i> ^[29]	Cirrhosis	394	317 (80.5%)	Not reported	Not reported
Gupta <i>et al</i> ^[30]	Cirrhosis	230	(61%)	(52%)	(9%)
Iwao <i>et al</i> ^[31]	Cirrhosis	476	254 (53%)	208 (43%)	46 (9%)
Carpinelli <i>et al</i> ^[32]	Cirrhosis	566	362 (64%)	192 (34%)	170 (30%)
Zaman <i>et al</i> ^[33]	Cirrhosis	120	74 (62%)	47 (39%)	27 (23%)
Primignani <i>et al</i> ^[34]	Cirrhosis	373	299 (80%)	127 (34%)	172 (46%)
Chaves <i>et al</i> ^[35]	Cirrhosis vs schistosomiasis	43	18 (81%) vs 7 (33%)	Not reported	Not reported
Merkel <i>et al</i> ^[36]	Cirrhosis	62	49 (79%)	29 (46%)	20 (32%)
Merli <i>et al</i> ^[37]	Cirrhosis, with mild portal hypertension	222	48 (21%)	43 (19%)	5 (2%)
Ito <i>et al</i> ^[38]	Cirrhosis	47	13 (27%)	10 (21%)	3 (6%)
De Palma <i>et al</i> ^[39]	Cirrhosis	37	23 (62%)	Not reported	Not reported
Menchén <i>et al</i> ^[40]	Cirrhosis	549	353 (64%)	275 (50%)	77 (14%)
Yüksel <i>et al</i> ^[41]	Cirrhosis	114 total	76 (66%)	38 (33%)	38 (33%)
Fontana <i>et al</i> ^[42]	Cirrhosis or bridging fibrosis from hepatitis C	1016	374 (37%)	345 (34%)	29 (3%)
Bresci <i>et al</i> ^[43]	Cirrhosis	85	36 (42%)	Not reported	Not reported
Akatsu <i>et al</i> ^[44]	End stage liver disease	29	19 (65.5%)	18 (62.1%)	1 (3.4%)
Zardi <i>et al</i> ^[45]	Cirrhosis	266	84 (31%)	Not reported	Not reported
Barakat <i>et al</i> ^[46]	Cirrhosis with portal hypertensive duodenopathy	105	105 (100%)	17 (16.2%)	88 (83.8%)
Bellis <i>et al</i> ^[47]	Cirrhosis	59	44 (76%)	16 (27%)	28 (47%)
Gravante <i>et al</i> ^[48]	Liver transplant candidates with cirrhosis	80	41 (51.2%)	Not reported	Not reported
Canlas <i>et al</i> ^[49]	Cirrhosis	19	13 (68.4%)	Not reported	Not reported
Kim <i>et al</i> ^[50]	Cirrhosis	83	48 (57.8%)	Not reported	Not reported
Higaki <i>et al</i> ^[51]	Cirrhosis	21	8 (38%)	Not reported	Not reported
Frenette <i>et al</i> ^[52]	Cirrhosis	50	45 (90%)	28 (56%)	17 (34%) moderate
Tarantino <i>et al</i> ^[53]	Cirrhosis	153	88 (57.5%)	Not reported	Not reported
Curvelo <i>et al</i> ^[54]	Cirrhosis	46	43 (93.4%)	21 (45%)	22 (47%)
Anegawa <i>et al</i> ^[55]	Cirrhosis	70	49 (70%)	32 (46%)	17 (24%)
Kumar <i>et al</i> ^[56]	Cirrhosis	254	140 (55%)	Not reported	Not reported
Kim <i>et al</i> ^[57]	Cirrhosis	331	298 (90%)	Mild 84 (25.4%)	214 (64.7%)
De Lisi <i>et al</i> ^[58]	Cirrhosis	611	448 (73.3%)	37.3%	36%
Abbasi <i>et al</i> ^[59]	Cirrhosis	102	87 (85%)	Not reported	Not reported
Ahmed <i>et al</i> ^[60]	Cirrhosis from hepatitis B or hepatitis C	360	300 (83%)	229 (64%)	71 (20%)
Garcia-Saenz-de-Sicilia <i>et al</i> ^[61]	Cirrhosis	105	72 (68.6%)	Not reported	Not reported
Abbasi <i>et al</i> ^[62]	Cirrhosis	217	172 (79.3%)	56 (25.8%)	116 (53.5%)
Aoyama <i>et al</i> ^[63]	Cirrhosis	60	13 (22%)	Not reported	Not reported
Laleman <i>et al</i> ^[64]	Cirrhosis with refractory chronic hepatic encephalopathy	36	13 (36%)	9 (25%)	4 (11%)
Giannini <i>et al</i> ^[65]	Cirrhosis and undergoing surgery for hepatocellular carcinoma	152	23 (15.1%)	Not reported	Not reported
Abdollahi <i>et al</i> ^[21]	Autoimmune hepatitis	60	27 (45%)	Not reported	Not reported
Aoyama <i>et al</i> ^[23]	Portal hypertension	119	35 (29%)	Not reported	Not reported
Aoyama <i>et al</i> ^[66]	Cirrhosis	134	42 (31%)	Not reported	Not reported
Zardi <i>et al</i> ^[67]	Cirrhosis without gastroesophageal varices	145	75 (51%)	45 (31%)	30 (20%)
Wu <i>et al</i> ^[68]	Cirrhosis	700	449 (64%)	Mild 208 (29.7%), moderate 160 (22.9%)	Severe 81 (11.6%)

PHG: Portal hypertensive gastropathy.

PHG had significantly higher HVPG (15.6 ± 4.6 mmHg) than patients with mild PHG (10.7 ± 4.1 mmHg) or no PHG (4.9 ± 1.7 mmHg) ($P < 0.001$). Merkel *et al*^[36] similarly reported in a small study that HVPG was significantly higher in patients with severe PHG as compared to mild or no PHG.

Primignani *et al*^[34] confirmed the correlation of PHG with severity of portal hypertension, by correlating PHG with presence and size of esophageal varices. The rate of PHG was significantly higher in patients with esophageal varices [80 of 104 patients (76.9%)]

than in patients without esophageal varices [51 of 84 (60.7%), $P < 0.007$]. The rate of PHG also significantly increased with increasing variceal size ($\chi^2 = 13.2$; $df = 1$, $P = 0.0003$). Abbasi *et al*^[62] reported a significantly positive correlation between esophageal variceal size and rate of PHG ($r = 0.46$; $P < 0.001$). Taranto *et al*^[29] reported more severe PHG in cirrhotic patients with more severe portal hypertension, as measured by esophageal intravariceal pressure. Iwao *et al*^[28] reported that patients with severe PHG had elevated HVPG, high hepatic sinusoidal resistance, and low hepatic blood

flow, all markers of severe portal hypertension. For example, patients without PHG had hepatic sinusoidal resistance of $1218 \pm 528 \text{ dyne} \times \text{s}^{-1} \times \text{cm}^{-5}$, patients with mild PHG had resistance of $1968 \pm 944 \text{ dyne} \times \text{s}^{-1} \times \text{cm}^{-5}$ ($P < 0.05$), and patients with severe PHG had resistance of $2082 \pm 672 \text{ dyne} \times \text{s}^{-1} \times \text{cm}^{-5}$ ($P < 0.01$). Presence of PHG was independent of patient age, sex, or cirrhosis etiology^[28].

As discussed below, other data supporting an association between PHG and portal hypertension include resolution of PHG after intervention to decrease portal hypertension, including pharmacotherapy^[74-78], transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation^[74].

Contrariwise, a decided minority of studies showed no significant association between severity of portal hypertension and rate of PHG^[8,9,16,26,28,30,31,47,54,67]. Curvêlo *et al.*^[54] found no significant difference in HVPG in cirrhotic patients with vs without PHG. Bellis *et al.*^[47] demonstrated similar findings. Among patients with portal hypertension from cirrhosis without esophageal varices, Zardi *et al.*^[67] reported that patients with PHG vs patients without PHG had similar mean portal vein diameter, splenic vein diameter, and portal flow volume, all markers of severity of portal hypertension. Erden *et al.*^[16] showed that the mean diameters of the left gastric, paraesophageal, and azygos veins, which are markers of portal hypertension, were not significantly different between patients with vs without PHG. The preponderance of data strongly suggest that the severity of portal hypertension is associated with the severity or frequency of PHG.

Cirrhotic vs non-cirrhotic portal hypertension:

Primary liver disease usually occurs in PHG, but is not a prerequisite for PHG provided another cause of portal hypertension exists. PHG can occur among patients with non-cirrhotic portal fibrosis (NCPF), extrahepatic portal vein obstruction (EHPVO), hepatic veno-occlusive disease, and schistosomiasis^[8,14,35,75,79].

The frequency of PHG appears to be higher in portal hypertension with cirrhosis than in portal hypertension without cirrhosis. Sarin *et al.*^[8] reported that patients with cirrhosis had a significantly higher frequency of PHG (37.1%) than that in patients with NCPF (16.7%; $P < 0.05$), or non-cirrhotic EHPVO (8.7%; $P < 0.01$) and had a more aggressive course of PHG with progression to more severe PHG with time. These phenomena are attributed to the worse liver function in patients with cirrhosis as compared to patients with NCPF or EHPVO^[8]. Chaves *et al.*^[35] similarly reported a higher incidence of PHG in patients with cirrhosis vs patients with portal hypertension from etiologies including schistosomiasis or postsinusoidal hypertension. Chaves *et al.*^[35] reported that PHG occurred in 18 (81.8%) of 22 patients with cirrhosis vs only 7 (33.3%) of 21 patients with portal hypertension from schistosomiasis ($P < 0.05$). Parikh *et al.*^[9] reported a non-significant trend of more frequent PHG in patients with cirrhosis [64 of 102 patients (63%)]

vs NCPF [7 of 16 patients (44%)], but the lack of statistical significance may have resulted from the small number of patients with NCPF.

Chaves *et al.*^[35] reported that the mosaic pattern was significantly more prevalent in patients with cirrhosis [12 of 22 patients (54.5%)] than in patients with schistosomiasis [2 of 21 patients (9.5%); $P < 0.05$]. Sarin *et al.*^[6] in a study of 50 patients with portal hypertension from various etiologies undergoing endoscopy, reported 6 (16.6%) of 36 patients with underlying cirrhosis had a mosaic pattern of PHG, whereas only 1 (8.5%) of 12 patients with EHPVO had a mosaic pattern of HPG (NS).

Cirrhosis etiology: Several research groups reported that the underlying etiology of cirrhosis did not affect PHG frequency or severity^[13,71,80]. For example, Abbasi *et al.*^[62] reported among 217 patients with cirrhosis that PHG was unassociated with cirrhosis etiology ($r = 0.056$; $P = 0.414$), among 144 patients with hepatitis C, 36 patients with hepatitis B, 21 patients with cryptogenic cirrhosis, 15 patients with hepatitis C and hepatitis B coinfection, and 1 patient with hepatitis B and hepatitis D coinfection. Kim *et al.*^[57] similarly did not find a correlation between cirrhosis etiology and severity of PHG in a prospective study of 331 patients with cirrhosis, including cirrhosis etiologies of alcohol in 250, hepatitis B in 68, hepatitis C in 15, and cryptogenic cirrhosis in 8. Gupta *et al.*^[30] in a study of 230 patients with cirrhosis and esophageal varices found no significant difference in the rate of PHG between patients with cirrhosis from alcohol [32 of 52 patients (62%)] vs cirrhosis from other causes [110 of 178 patients (62%), $P = \text{NS}$]. Iwao *et al.*^[31] in an endoscopic study of 47 patients with histologically-proven cirrhosis reported no significant differences in etiology of cirrhosis between patients without PHG vs patients with mild or severe PHG.

Iwao *et al.*^[31] reported no association between etiology of cirrhosis and PHG severity. The etiologies of cirrhosis in this study included 7 from alcoholism vs 8 from chronic hepatitis in patients without PHG, 5 from alcoholism vs 10 from chronic hepatitis in patients with mild PHG, and 8 from alcoholism vs 9 from chronic hepatitis in patients with severe PHG (NS).

Liver disease duration: Generally, duration of liver disease positively correlates with development of PHG^[5]. Merli *et al.*^[37] reported a cumulative incidence of 3% at 1 year, 10% at 2 years, and 24% at 3 years. Most cases were mild, with only 10% of cases reported as severe PHG in cirrhotic patients undergoing esophagogastroduodenoscopy (EGD) to screen for esophageal varices. Primignani *et al.*^[34] reported that the prevalence of PHG was only 56% in patients with newly diagnosed cirrhosis, rose to 75% in patients with previously diagnosed cirrhosis and no prior variceal bleeding, and rose further to 91% in patients with previously diagnosed cirrhosis and prior variceal bleeding treated with sclerotherapy ($\chi^2 = 34.25$; $df = 1$;

$P < 0.0001$). The frequency of PHG increased by 46% after 5 years of follow-up in patients with cirrhosis^[34]. In 30%-60% of cases, preexistent PHG remained stable with time^[72], but it can fluctuate in severity with time, with progression in 30%, and regression in 20% of cases^[25,34,37]. Child-Pugh stage C cirrhosis was associated with faster progression of PHG^[34].

Liver disease severity: Numerous studies reported PHG is correlated with liver disease severity, as measured by Child-Pugh stage^[8,9,29,35,37,55,57,67]. The reported strength of this correlation is variable. Some studies showed correlation between all stages of cirrhosis and PHG, whereas other studies showed correlation only for specific stages of cirrhosis. Sarin *et al.*^[8] reported an 87% prevalence of PHG in patients with Child-Pugh stage C, vs only 13% prevalence in patients with Child-Pugh stage A. Another study reported that only Child-Pugh stage C was independently associated with PHG (OR = 2.68; 95%CI: 1.16-6.20, $P = 0.021$)^[56]. Merli *et al.*^[37] reported, in a study of 48 patients with PHG among 222 patients with cirrhosis, that Child-Pugh stage B or C, and presence of esophageal varices were independent risk factors for developing PHG. De Lisi *et al.*^[58] reported a significantly higher prevalence of PHG in Child-Pugh stages B or C, as compared to stage A. Zardi *et al.*^[67] reported that cirrhotic patients without esophageal varices with severe PHG had significantly more frequently Child-Pugh stage C than patients with mild PHG. In another study, the MELD (model for end-stage liver disease) score was significantly correlated with PHG severity (mean MELD score in patients without PHG = 7.6 ± 1.7 , in patients with mild PHG = 10.2 ± 4.0 , and in patients with severe PHG = 11.3 ± 3.5 ; $P < 0.001$)^[57]. In the HALT-C trial, hypoalbuminemia and hyperbilirubinemia, biochemical markers of advanced liver disease, were independent predictors of PHG in a logistic regression model (OR = 0.53, 95%CI: 0.37-0.76 for hypoalbuminemia; OR = 1.77, 95%CI: 1.25-2.51, for hyperbilirubinemia). Markers of portal hypertension (thrombocytopenia) and of insulin resistance (hyperglycemia) were also significant independent predictors of PHG.

Contrariwise, a minority of studies found no correlation between liver disease severity, as determined by Child-Pugh stage, and presence or severity of PHG^[34,36,40,47,54,62,70,79]. For example, Primignani *et al.*^[34] reported the prevalence of severe PHG was lowest in Child-Pugh stage C. In the NIEC study, patients with Child-Pugh stage B had a higher prevalence of PHG than patients with stages A or C. Zardi *et al.*^[67] reported no significant differences in Child-Pugh stage or in MELD score among cirrhotic patients with vs without PHG. The preponderance of the data, however, suggest that severity of cirrhosis, as measured by Child-Pugh score, is correlated with frequency of PHG.

Correlation with varices: Many studies report a correlation between the presence and size of esopha-

geal varices and severity of PHG. For example, among the 188 of 373 patients with cirrhosis not undergoing variceal sclerotherapy in the NIEC study, the prevalence of PHG was significantly higher in patients with esophageal varices [80 of 104 patients (77%)] than in patients without esophageal varices [51 of 84 patients (61%); $P = 0.007$]; and the prevalence of PHG significantly increased with increasing variceal size ($\chi^2 = 13.2$; $P < 0.0003$)^[34]. Numerous other studies also demonstrated significant correlation between presence of esophageal varices and PHG, and several studies also demonstrated significant correlations between variceal size and PHG^[9,13,29,42,56,57,62]. For example, Abbasi *et al.*^[62] reported that esophageal variceal size was significantly correlated with PHG frequency among 217 cirrhotic patients ($r = 0.46$; $P < 0.001$).

However, a few studies showed no correlation between presence or size of varices and PHG^[26,28,30,47]. All these negative studies but one were relatively small. Gupta *et al.*^[30] reported no significant association between frequency of PHG and size of esophageal varices among 230 cirrhotic patients. Similarly, in a study of 59 patients with cirrhosis, Bellis *et al.*^[47] showed a non-significant trend towards more severe PHG in patients with large vs small varices. For example, three (50%) of 6 patients without esophageal varices had PHG, 6 of 10 patients (60%) with small varices had PHG, 19 of 25 patients (76%) with medium-sized varices had PHG, and 16 of 18 patients (89%) with large varices had PHG (NS). Iwao *et al.*^[28] further reported that the frequency of PHG was not correlated with esophageal variceal size. The mean grade of gastroesophageal varices was 1.4 ± 0.9 for no PHG, 2.0 ± 0.9 for mild PHG, and 1.9 ± 1.0 for severe PHG (all NS), and the mean grade of gastric varices was 0.5 ± 0.8 for no PHG, 1.3 ± 1.3 for mild PHG, and 0.9 ± 1.2 for severe PHG (all NS).

Location of varices: Regarding variceal location, Sarin *et al.*^[8] reported in a study of 107 patients with cirrhosis, NCPF or EHPVO, that PHG was significantly more common in patients with coexistent gastric and esophageal varices as compared to solely esophageal varices. PHG occurred in 15 (42%) of 36 patients with concomitant esophageal and gastric varices, but occurred in only 8 (11%) of 71 patients with solely esophageal varices ($P < 0.01$). Likewise, Gupta *et al.*^[30] reported a significantly higher prevalence of PHG in patients with esophageal and gastric varices [74 of 107 patients (69%)] compared to solely esophageal varices [68 of 123 patients (55%), $P < 0.05$].

Iwao *et al.*^[31] reported a significantly higher incidence of PHG in cirrhotic patients with esophageal varices as compared to fundal gastric varices. Merkel *et al.*^[36] reported that patients with severe PHG localized to the gastric body or fundus had significantly higher HVPG than patients with severe PHG localized to the gastric antrum.

Portal hypertension is usually associated with porto-

Table 3 Effects of variceal ligation on frequency of portal hypertensive gastropathy

Ref.	No. of patients and etiology	Study type	PHG rate before variceal ligation	PHG aggravation after variceal ligation	P value of pre vs post EVL
Hou <i>et al</i> ^[73]	90 patients with cirrhosis and recent variceal bleeding, 46 patients underwent EVL	Randomized, controlled trial	No PHG-4, mild PHG-33, severe-PHG-9	At eradication: 17/37; 17/37 (45.9%) in EVL; at 3 mo: 17/30 (56.7%); at 6 mo 18/29 (62.1%)	$P > 0.05$
Elnaser <i>et al</i> ^[80]	125 patients with upper GI bleeding undergoing variceal ligation, followed for mean of 31 mo	Retrospective study	22/125 (17.6%)	50/125 (50%)	$P < 0.05$
Yüksel <i>et al</i> ^[41]	114 patients with cirrhosis and portal hypertension undergoing EVL in 85 patients	Retrospective study	27/85 (31.8%) none; 28/85 (32.9%) mild; 30/85 (35.3%) severe	14/85 (16.5%) none; 30/85 (35.3%) mild; 41/85 (48.2%) severe	$P < 0.05$
Lo <i>et al</i> ^[81]	77 patients with bleeding from EV underwent variceal ligation and were randomized to receive propranolol (37/77) or control (40/77); patients with severe PHG prior to treatment excluded from the study	Prospective, randomized, controlled trial	Control group: 7/40 (17%); propranolol group: 8/37 (22%)	At variceal ligation: Control group: 67% (does not state number); Propranolol group: 31% (number not stated); 6 mo after treatment: Control group: 85% (number not stated) propranolol group: 48% (number not stated)	Pre vs post ligation, both groups; $P < 0.05$; frequency of PHG significantly higher in control group post ligation when compared to propranolol group; $P = 0.002$
de la Peña <i>et al</i> ^[82]	93 patients with history of variceal hemorrhage and cirrhosis, randomized to receive either EVS (46/88) or EVL (42/88); 5 patients excluded due to diagnosis of hepatoma, non-cirrhotic portal hypertension or portal vein thrombosis	Randomized, prospective study	Not reported	PHG significantly worsened in 23 patients, including 17 patients undergoing EVL	$P < 0.01$

PHG: Portal hypertensive gastropathy; EVL: Endoscopic variceal ligation; EVS: Endoscopic variceal sclerotherapy.

systemic collateral circulation, commonly including esophageal varices, gastric varices, and abdominal or umbilical or hemorrhoidal vein dilatation; and uncommonly including splenorenal, gastric, renal, retroperitoneal, or cardiac angle venous shunts. Wu *et al*^[68] reported that the rate of moderate or severe PHG was higher in patients with common collaterals [296 of 439 patients (67.4%)] vs uncommon collaterals [70 of 118 patients (59.3%)], but this difference was not statistically significant.

In 2007, Zardi *et al*^[45] proposed that PHG is promoted by minimal collateral circulation because a significant collateral circulation would otherwise reduce portal pressure and gastric mucosal congestion. They found that the portal vein diameter in cirrhotic patients was larger in patients with PHG and no esophageal varices (13.0 ± 2.6 mm) than in patients with F1 esophageal varices (12.6 ± 2.3 mm) or F2 esophageal varices (12.9 ± 2.0 mm) (NS). They further supported this concept by finding that patients with portal vein diameter < 12 mm have a significantly higher prevalence of F1 and F2 esophageal varices than patients with a portal diameter between 12-13 mm, and argued that the absence of hepatofugal collateral circulation created by flow inversion, in patients without esophageal varices, left the entire pressure gradient over the portal vein^[45].

Esophageal variceal eradication: Numerous studies demonstrated that PHG increased in incidence and that preexistent PHG increased in severity after eradication of esophageal varices by either endoscopic variceal ligation

(Table 3)^[41,73,80-82] or endoscopic variceal sclerotherapy (Table 4)^[8,10,11,25,30,41,73,81-83] in cirrhotic patients with portal hypertension. Both phenomena also occurred after endoscopic variceal eradication in patients with non-cirrhotic portal hypertension, as shown in two studies in pediatric patients with EHPVO. For example, Poddar *et al*^[83,84] reported in a prospective study of 274 children undergoing surveillance EGD after endoscopic sclerotherapy for EHPVO that the number of patients with PHG increased from 46 (24.7%) at baseline to 95 (51.6%) after sclerotherapy among 186 patients completing the study ($P < 0.001$). Likewise, Itha *et al*^[11] reported that the rate of PHG increased from 12% to 41% after endoscopic sclerotherapy ($P < 0.001$) in a prospective study of 163 children undergoing surveillance EGD at 3 and 6 mo after endoscopic sclerotherapy. In the study by Sarin *et al*^[10], 86 (9%) of 967 patients with prior variceal bleeding treated with endoscopic sclerotherapy, had PHG at EGD, of whom 22 (26%) had PHG before variceal eradication and 64 (74%) developed PHG after variceal eradication.

PHG also increases in frequency after angiographic variceal obliteration. Duan *et al*^[85] reported *de novo* PHG developed in 13 of 34 patients (38%) after percutaneous transhepatic variceal embolization for massive esophago-gastric variceal hemorrhage.

These phenomena are attributed to increased portal pressure and flow after eradication of esophageal varices because of redistribution of residual blood flow that had passed through the previously patent varices^[5,41,45,81,86-90]. Itha *et al*^[11] concluded that the significant increase in

Table 4 Effects of variceal sclerotherapy on frequency of portal hypertensive gastropathy

Ref.	No. of patients and etiology	Study type	PHG before procedure	PHG aggravation after procedure	P value
Hou <i>et al</i> ^[73]	90 cirrhotic patients with recent variceal bleeding; EVS 44, EVL 46	Randomized, controlled trial	Pre EVS group: 6 none/24 mild/14 severe; pre EVL group: 4 none/33 mild/9 severe; total: 10 none/57 mild/23 severe	At eradication: 14/29 (48.3%) in EVS; 17/37 (45.9%) in EVL; at 3 mo: 15/26 (57.7%) in EVS; 17/30 (56.7%) in EVL; at 6 mo 15/25 (60%) in EVS; 18/29 (62.1%) in EVL	Non-significant difference in PHG aggravation between EVS and EVL; <i>P</i> > 0.05
Itha <i>et al</i> ^[11]	163 children with extrahepatic portal vein obstruction presenting with variceal bleeding underwent endoscopic injection sclerotherapy	Not reported	12% overall PHG (actual number not stated), 1 patient with severe PHG	41% overall PHG (actual number not stated), 12 patients with severe PHG	<i>P</i> < 0.001 for overall PHG; <i>P</i> < 0.001 for severe PHG
Poddar <i>et al</i> ^[83]	186 children with extrahepatic portal vein obstruction presenting with variceal bleeding undergoing endoscopic sclerotherapy, and mean follow up of 38 ± 30 mo	Retrospective study	PHG: 46/186 (24.7%), severe PHG: 6/186 (3.2%)	PHG: 96/186 (51.6%), severe PHG: 29/186 (15.6%)	<i>P</i> < 0.001 for overall PHG; <i>P</i> < 0.05 for severe PHG
Yüksel <i>et al</i> ^[41]	114 patients with cirrhosis and portal hypertension undergoing EVS (29/114) or EVL (85/114)	Retrospective study	Pre EVS group: 11/29 (37.9%) none; 10/29 (24.5%) mild; 8/29 (27.6%) severe; pre EVL group: 27/85 (31.8%) none; 28/85 (32.9%) mild; 30/85 (35.3%) severe	Post EVS group: 4/29 (13.8%) none; 8/29 (27.6%) mild; 17/29 (58.6%) severe; post EVL group: 14/85 (16.5%) none; 30/85 (35.3%) mild; 41/85 (48.2%) severe	Pre EVS <i>vs</i> post EVS; <i>P</i> < 0.05; pre EVL <i>vs</i> post EVL; <i>P</i> < 0.05; pre EVS <i>vs</i> pre EVL; <i>P</i> > 0.05; post EVS <i>vs</i> post EVL; <i>P</i> > 0.05
Sarin <i>et al</i> ^[10]	967 patients with variceal bleeding underwent endoscopic sclerotherapy; out of whom 88 patients fulfilled the inclusion criteria (including presence of endoscopic lesions consistent with PHG or GAVE, before or within 4 wk after obliteration) were prospectively followed (out of whom 2 had only GAVE)	Prospective study	22 patients had PHG prior to EVS; 2/22 transient (9%); 17/22 persistent (77%); 3/22 progressive (14%)	Additional development in 64 patients post procedure, 28/64 transient (44%), 31/64 persistent (48%), 5/64 progressive (8%)	Only statistically significant difference was the transient PHG that disappeared in 28 (44%) of patients in the group that developed PHG post procedure; <i>P</i> < 0.05
Gupta <i>et al</i> ^[30]	230 patients with liver cirrhosis; of which 44 underwent variceal eradication with sclerotherapy	Prospective study	24/44 (54%)	33/44 (75%)	<i>P</i> < 0.05
Sarin <i>et al</i> ^[8]	107 patients with portal hypertension presenting with variceal bleeding that underwent sclerotherapy with mean follow-up of 23.2 ± 3.4 mo	Prospective study	4/107 (3.7%)	21 additional patients, 25/107 (23%)	Does not state if this was statistically significant
de la Peña <i>et al</i> ^[82]	93 patients with history of variceal hemorrhage and cirrhosis, randomized to receive either EVS (46/88) or EVL (42/88); 5 patients were excluded due to diagnosis of hematoma, non-cirrhotic portal hypertension or portal vein thrombosis	Prospective study	Not reported	PHG worsened in 23 patients total; statistically significantly more in EVL group than EVS group (17 <i>vs</i> 6 patients respectively)	<i>P</i> < 0.01
D'Amico <i>et al</i> ^[25]	212 cirrhotic patients of which 75 had an episode of variceal bleeding and were treated with sclerotherapy; 137 without bleeding were not treated with sclerotherapy	Prospective study	No EVS group at admission: 104/137 (75%) none; 28/137 (20%) mild; 5/137 (4%) severe; EVS group at admission: 50/75 (66%) none; 17/75 (22%) mild; 8/75 (11%) severe	No EVS group at end of study 69/137 (50%) none; 61/137 (45%) mild; 7/137 (5%) severe; EVS group at end of study: 13/75 (17%) none; 49/75 (65%) mild; 13/75 (17%) severe	The conclusion was that sclerotherapy is a significant indicator of the risk of PHG in a multivariate analysis (<i>P</i> = 0.00032)

PHG: Portal hypertensive gastropathy; EVL: Endoscopic variceal ligation; EVS: Endoscopic variceal sclerotherapy.

frequency and severity of PHG after variceal eradication resulted from decreasing collateral blood flow through esophageal varices causing increasing PHG from gastric mucosal congestion. This mechanism is supported by

finding that gastric mucosal blood flow increases after variceal ligation^[91]. Another theory is that delayed gastric emptying after sclerotherapy from extravasation of sclerosant, may cause development of PHG^[69]. No direct

Table 5 Well-established, important risk factors for portal hypertensive gastropathy

Parameters	Ref.
Portal hypertension	
Non-cirrhotic portal hypertension	[8,14]
Cirrhotic portal hypertension	[8,9,34]
Cirrhosis	
Longer duration of cirrhosis	[34,71]
Greater severity of cirrhosis	[55,67]
Greater size of esophageal varices	[34,62]
Eradication of esophageal varices	
Endoscopic therapies	
Endoscopic variceal ligation	[11,41]
Endoscopic sclerotherapy	[11,83]
Angiographic	
Percutaneous transhepatic variceal embolization	[85]

evidence exists for delayed gastric emptying in PHG^[71].

Data on which technique of endoscopic variceal eradication leads to quantitatively more *de novo* PHG is contradictory. Most studies showed no differences in frequency or severity of PHG after variceal ligation vs sclerotherapy^[19,34,41,73,92,93], but some studies showed worse outcomes after variceal ligation^[82,93,94], while some other studies showed worse outcomes after sclerotherapy^[95].

De novo PHG after variceal obliteration is often transitory and less severe than PHG that predated the variceal obliteration^[10,73]. For example, Sarin *et al.*^[10] reported in a study of 84 patients followed for a mean of 25 ± 14 mo that PHG resolved in 28 (44%) of 64 patients who developed PHG after sclerotherapy, but resolved in only 2 (9%) of 22 patients who had PHG present before sclerotherapy ($P < 0.05$). Hou *et al.*^[73] similarly reported that the increased severity of PHG after variceal obliteration was generally transitory and returned to baseline status. The return to baseline severity of PHG was significantly faster after variceal ligation than after sclerotherapy ($P = 0.03$), attributed to ligation achieving subtotal variceal obliteration and permitting faster redistribution of blood flow^[10].

Some investigators believe the higher rate of PHG in patients undergoing endoscopic variceal sclerotherapy merely reflects a longer duration of portal hypertension, more advanced liver disease, or more severe portal hypertension in patients selected to undergo variceal sclerotherapy compared to controls rather than the performance of sclerotherapy *per se*^[34,78,96]. Primignani *et al.*^[34,97] demonstrated an almost identical increase in frequency of PHG with time in patients undergoing vs not undergoing sclerotherapy, and suggested that PHG evolved identically with time regardless of performance vs nonperformance of sclerotherapy.

Additional risk factors: PHG severity is significantly associated with thrombocytopenia or splenomegaly^[42,57,58]. In a prospective study of 331 cirrhotic patients performed in South Korea, PHG severity was correlated with splenic diameter: Splenic diameter with

severe PHG = 13.1 ± 2.4 cm, diameter with mild PHG = 12.2 ± 2.5 cm, and diameter with no PHG = 10.7 ± 2.9 cm, $P < 0.001$ ^[57]. In this study, PHG severity was inversely correlated with platelet count: count with no PHG = 174600 ± 109400 platelets/mm³, count with mild PHG = 132000 ± 100700 platelets/mm³, count with severe PHG = 102800 ± 68800 platelets/mm³ ($P < 0.001$). Among 1016 patients with bridging fibrosis or compensated cirrhosis undergoing EGD in the HALT-C trial, including 374 (37%) with PHG, PHG was negatively correlated with platelet count in a logistic regression model (negative estimate: -0.00407 , OR = 0.99 , 95%CI: $0.99-0.998$; $P = 0.0007$)^[42].

In one study, PHG in patients with chronic liver disease was correlated with increasing thickness of the lesser omentum, and presence of a splenorenal shunt^[22]. This study found that PHG frequency was not associated with severity of hypersplenism^[62]. The HALT-C trial showed no association between prevalence or severity of PHG and lifetime alcohol consumption, nonsteroidal anti-inflammatory drugs (NSAIDs) use, COX- (cyclooxygenase-) 2 inhibitor use, or smoking^[42]. The lack of association with alcoholism may reflect the need for near abstinence from alcohol to have enrolled in the clinical trial; at study enrollment 86% of patients reported abstinence and 14% reported minimal drinking of alcohol. Table 5^[8,9,11,14,34,41,55,62,67,71,83,85] lists well-established risk factors for PHG; Table 6^[11,41,44,55,75-77,83,85,98-107] lists therapies that affect the severity of PHG or the risk of bleeding from PHG, and Table 7^[8,14,28,30,35,42,84,108-110] lists the factors that do not affect the risk of PHG.

Pathogenesis

Hemodynamic changes: The pathogenesis of PHG is inadequately understood^[96]. Hemodynamic changes, especially increased portal pressure, are the suspected underlying cause because PHG develops only with established portal hypertension^[72]. However, portal hypertension cannot be the sole factor because many patients with portal hypertension do not develop PHG^[36,111]. Hemodynamic changes in patients with portal hypertension lead to hyperdynamic congestion with a change in gastric mucosal blood flow^[112], that leads to activation of cytokines, growth factors, and hormones that perpetuate this hyperdynamic gastric circulation^[113]. Vascular congestion in PHG alters the gastric microcirculation, but the nature and extent of this alteration is somewhat controversial. The hyperdynamic circulation of portal hypertension is characterized by increased intrahepatic vascular resistance, generalized splanchnic vasodilatation, decreased mean arterial pressure, decreased systemic vascular resistance, increased gastric blood flow, and most likely decreased gastric mucosal flow^[110,114,115]. Hashizume *et al.*^[116] reported that cirrhotic patients have dilated small gastric blood vessels, including arterioles, precapillaries, capillaries, submucosal veins, and subserosal veins, with decreased arteriovenous resistance and straightening of arterioles.

Table 6 Therapies affecting the severity or the risk of bleeding from portal hypertensive gastropathy

Therapies reducing severity of PHG	Ref.
TIPS	[76,77,98]
Transcatheter splenic arterial embolization	[99]
Surgical shunt	
Portocaval shunt	[100]
Central splenorenal shunt	[101]
Laparoscopic splenectomy (in patients with hypersplenism)	[55]
Liver transplantation	[44]
Therapies reducing risk of bleeding from PHG	
TIPS	[75,98,102]
Surgical shunt (portocaval or splenorenal)	[100,101]
Nonselective β -adrenergic receptor antagonists (<i>e.g.</i> , propranolol)	[103 (in rats),104]
Somatostatin family of drugs	
Somatostatin	[105]
Octreotide	[106]
Vasopressin family of drugs	
Vasopressin	[106]
Terlipressin	[107]
Therapies that increase incidence or risk of bleeding from PHG	
Endoscopic therapies for varices	
Variceal ligation	[11,41]
Variceal sclerotherapy	[11,83]
Interventional angiography	
Percutaneous transhepatic variceal embolization	[85]

TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy.

This hyperdynamic circulation impairs gastric mucosal defense mechanisms, causes release of proinflammatory mediators, and inhibits growth factors which render gastric mucosa more susceptible to injury^[67,117] and impair mucosal healing^[113,114,118,119]. This vulnerable mucosa becomes predisposed to bleeding^[117,120]. Decreased gastric mucosal perfusion may explain the increased rate of erosions, ulcers, and bleeding in PHG^[118]. Abnormal regulation of the gastric microcirculation in PHG may render gastric mucosa more vulnerable to hypoxia^[112,122], and more susceptible to noxious gastric factors, such as aspirin and ethanol^[123-125].

Misra *et al.*^[126] showed that gastric mucosal capillaries, obtained by endoscopic mucosal biopsies, have a much thicker wall in patients with cirrhosis than in healthy volunteers. Ichikawa *et al.*^[127] reported a narrower diameter in gastric mucosal capillaries and less capillary angiogenesis, measured as percentage of buds in microvessels, after exposure to ethanol in individuals with PHG as compared to healthy controls. Tarnawski *et al.*^[121] reported prominent cytoplasm in endothelial cells of mucosal microvessels, that narrowed the capillary lumina, in rats with PHG. This finding was confirmed by electron microscopy which showed significantly larger cytoplasmic and pinocytic vesicular areas and increased capillary basement membrane thickness. Additionally, there was arterialization of submucosal veins and thickening of arterioles in the muscularis mucosae and submucosa^[121].

Table 7 Factors not affecting risk of portal hypertensive gastropathy

Factors not affecting risk of portal hypertensive gastropathy	Ref.
Etiology of cirrhosis	[8,28,30]
Etiology of non-cirrhotic portal hypertension	[8,14,35,83,108]
Alcoholism	[30,42]
NSAID use	[42]
Use of COX-2 inhibitors	[42]
Smoking tobacco	[42]
Gastric infection with <i>Helicobacter pylori</i>	[109,110]

NSAID: Nonsteroidal anti-inflammatory drug; COX-2: Cyclooxygenase-2.

The level of gastric mucosal blood flow in PHG is controversial. Most studies reported decreased mucosal blood flow in patients with PHG^[76,128-131], whereas several studies reported increased gastric mucosal blood flow in experimental animals and in humans with PHG^[132-136]. Makhija *et al.*^[118] described in PHG a decrease in gastric mucosal blood flow, an increase in the submucosal and muscular layer blood flow, and a net increase in total gastric blood flow. Mezawa *et al.*^[76] using a laser Doppler flowmeter to measure gastric mucosal blood flow and near-infrared endoscopy to measure total gastric blood flow, reported decreased mucosal blood flow and increased total blood flow in patients with PHG. These results reversed after undergoing TIPS, with an increase in mucosal blood flow and a decrease in total blood flow. These findings support the hypothesis of decreased mucosal blood flow in patients with PHG. Ohta *et al.*^[113] reported a decrease in superficial mucosal blood flow rendering mucosa more susceptible to injury, but noted a net increase in total gastric blood flow. Variability in study results arise from study biases including chronic anemia in some patients, variable measurement techniques, different techniques of applying endoscopic probes in laser-Doppler flowmetry, and differences in gastric mucosal angioarchitecture^[113]. Laser-Doppler flowmetry, moreover, has limited utility in clinical practice^[137,138].

Portal hypertension increases the splenic circulation^[139]. Pan *et al.*^[79] reported that PHG severity was strongly correlated with hypersplenism ($P = 0.003$). However, Abbasi *et al.*^[62] did not show this correlation. The difference between these studies may reflect use of different classifications for PHG. Figure 1 describes the hypothesized pathophysiology of PHG. This current mechanism is currently sketchy and likely incomplete.

Patients with secondary polycythemia A have decreased blood flow and oxygen carrying capacity because of sluggish movement of viscous blood; this phenomenon produced endoscopic and histopathologic findings of congestive gastropathy similar to those in PHG that reversed after the patient underwent serial phlebotomies to reverse the polycythemia^[140].

Molecular mechanisms: Numerous molecular and cellular mechanisms have been investigated regarding

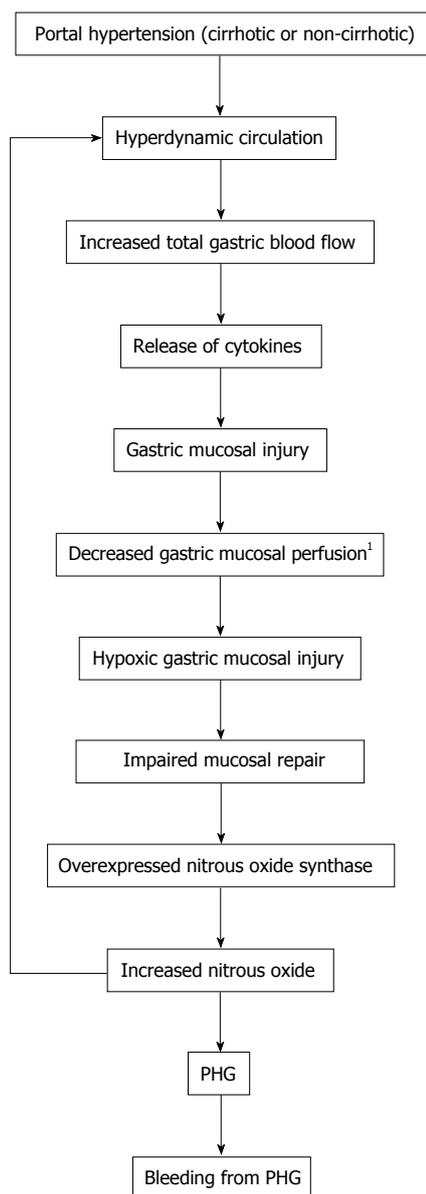


Figure 1 Hypothesized mechanism of portal hypertensive gastropathy. ¹The finding of decreased gastric mucosal perfusion in PHG is somewhat controversial (see text). PHG: Portal hypertensive gastropathy.

the pathogenesis of PHG.

Apoptosis: Wu *et al.*^[141] showed that rats with PHG had increased gastric mucosal apoptosis and decreased mucosal proliferation. Recently, a p53-upregulated modulator of apoptosis (PUMA) was reported markedly induced in gastric mucosa in patients or mouse models of PHG. PUMA is modulated by endoplasmic reticulum - stress-induced mucosal epithelial apoptosis in PHG^[142]. This effect could promote mucosal injury in PHG.

Free radicals and antioxidants: Kaur *et al.*^[143] showed elevated levels of injurious free radicals and lysosomal enzymes and decreased levels of protective antioxidant enzymes in gastric mucosal homogenates from rats with portal hypertension. Kawanaka *et al.*^[144] showed impaired endoplasmic reticulum serine/

threonine kinase-2 (ERK2) activation after oxidative stress in rat gastric mucosa; ERK2 normally protects against cellular stress by inducing cell proliferation in gastric mucosa. Kinjo *et al.*^[145] showed that enhanced nitration of ERK by peroxynitrite is involved in impaired MAPK (ERK) signaling in PHG, which impairs mucosal healing and promotes mucosal injury. The levels of lipid peroxide and nitrotyrosine that tend to promote gastric injury increased significantly in rats with PHG as compared to controls.

Mucin: Wang *et al.*^[146] reported significantly reduced expression of mucin mRNA in rat models of portal hypertension induced by partial portal vein ligation. Decreased mucin production may impair gastric mucosal protection. Rats with portal hypertension had significantly greater injury to gastric mucosa than healthy controls after exposure to gastrototoxic compounds. Tomikawa *et al.*^[135] reported decreased mucosal gel layer thickness, surface epithelial cell intracellular pH, and oxygenation of gastric mucosal surface in rats with PHG.

Angiogenesis: As aforementioned, the number of angiogenic buds decreased after injury to PHG mucosa. This phenomenon may decrease the reparative capacity of PHG mucosa^[127]. However, Tsugawa *et al.*^[136] reported humans with PHG had increased vascular endothelial growth factor (VEGF), a potent angiogenic factor. Additionally, rats with PHG had a significant decrease in the SaO₂ and PaO₂ of the arterial blood gas, and increased levels of VEGF, proliferating cell nuclear antigen (PCNA) expression, and gastric mucosal blood flow in gastric mucosa. They proposed that gastric mucosal hypoxia in portal hypertension and elevation of VEGF and PCNA levels might accelerate mucosal angiogenesis and increase blood flow^[147].

Tumor necrosis factor alpha: Tumor necrosis factor alpha (TNF- α) may directly contribute to the hyperdynamic circulation in PHG. Patients and animal models with portal hypertension had an elevated TNF- α level which stimulated release of nitric oxide (NO) and prostacyclin, important mediators of a hyperdynamic circulation^[148]. For example, in one study, 96 healthy rats were injected with either anti-TNF- α polyclonal antibodies or placebo before surgically creating portal vein stenosis (PVS) to induce portal hypertension and 4 d after in the short-term inhibition group and 1, 4, 7 and 10 d after PVS in the long term-inhibition group. Anti-TNF- α treated PVS rats exhibited lower serum levels of TNF- α , which normally stimulates the synthesis of NO and prostacyclin, and exhibited lower serum levels of nitrates and nitrites and of 6-keto-PGF-1- α (6-keto-PGF_{1 α}), used to monitor NO and prostacyclin release, respectively. The combined nitrate and nitrite level was significantly reduced from 68 \pm 9 nmol/mL in controls to 42 \pm 8 nmol/mL in the short-term inhibition group ($P < 0.05$), and from 66 \pm 6 nmol/mL in controls to 44 \pm 4 nmol/mL in the long-term inhibition group (P

< 0.05). Similarly the 6-keto-PGF_{1α} was significantly reduced from 484 ± 92 pg/mL in the controls to 174 ± 12 pg/mL in the short-term inhibition group (*P* < 0.05), and from 522 ± 98 pg/mL in the controls to 169 ± 18 (SD) pg/mL in the long-term inhibition group (*P* < 0.05). Kaviani *et al.*^[149] reported that TNF-α increased by 50% and inducible nitric oxide synthase (iNOS) mRNA levels increased by 300% in gastric strips after ligating the portal vein in rats (*P* < 0.01 for both). These data are consistent with TNF-α playing a role in the hyperdynamic circulation in PHG *via* NO and prostacyclin.

Baseline constitutional NOS (cNOS) mRNA expression increased by 75% in the PHG group as compared to placebo (*P* < 0.01)^[149]. NOS was significantly reduced after injecting a TNF-α neutralizing antibody during incubation of mucosal strips from portal hypertensive rats; the expression of inducible NOS mRNA levels was incrementally decreased by 40%, 70% and 80% after 1, 2, and 6 h of incubation, respectively (*P* < 0.05)^[149]. Ohta *et al.*^[150] similarly successfully used TNF-α antibody to normalize gastric mucosal blood flow in rats with PHG and to significantly reverse overexpression of gastric NOS isoform 3. In PHG rats, treatment with TNF-α antibody significantly reduced the elevated NOS isoform 3 mRNA expression by 48% (*P* < 0.01). Moreover, administration of thalidomide, which enhances TNF-α mRNA degradation, decreased levels of TNF-α and NOS in animals with portal hypertension produced by partial portal vein ligation^[114].

Nitric oxide: Patients with portal hypertension and PHG have increased serum levels of NO, a potent vasodilator released by endothelial cells. Ohta *et al.*^[151] demonstrated gastric cNOS significantly increased, by 67%, in portal hypertensive rats, experimentally produced by portal vein and splenic vein occlusion, as compared to sham-operated rats at 14 d after surgery (*P* < 0.05). In portal hypertensive rats, cNOS fluorescence intensity was significantly higher in endothelia of submucosal veins [96.2 ± 5.9 (SD) U] as compared to endothelia of mucosal collecting veins (69.5 ± 1.7 (SD) U, *P* < 0.01), or endothelia of veins of muscularis mucosae (55.7 ± 10.0 U, *P* < 0.01). The average fluorescence area in submucosal vein endothelia was significantly higher in portal hypertensive rats than in normal controls (1038.5 ± 459.5 (SD) μm² vs 372.4 ± 180.3 (SD) μm², *P* < 0.01). This finding may provide a molecular mechanism for submucosal vascular dilation in the hyperdynamic circulation in PHG. In another study, gastric mucosal cNOS levels were significantly higher in patients with cirrhosis and severe PHG compared to healthy controls [125.4 ± 4.3 (SD) pmol/mg protein/minute vs 88 ± 8.6 (SD) pmol/mg protein/minute, *P* < 0.002]. Likewise, gastric mucosal iNOS levels were significantly higher in patients with cirrhosis and severe PHG than in healthy controls [259.7 ± 5.5 (SD) pmol/mg protein/min vs 130.8 ± 6.6 (SD) pmol/mg protein/min, *P* < 0.0001]^[152]. Serum nitrate/nitrite levels were 30.1 ± 3.2 nmol/mL in the first group vs 15.5 ± 0.09 (SD) nmol/mL in the

second group (*P* < 0.001)^[152]. In another study, iNOS and cNOS levels were also higher in gastric mucosa of patients with PHG than in controls^[153], and were significantly higher in patients with severe PHG as compared to patients with mild or no PHG^[154]. Nitrous oxide may underlie the gastric vascular dilation^[152], and hyperdynamic circulation in PHG^[148].

However, Lee *et al.*^[155] reported administration of aminoguanidine, an iNOS inhibitor, successfully corrected the hyperdynamic circulation without affecting PHG, suggesting that iNOS and NO are important in the hyperdynamic circulation in portal hypertension, but play a limited role in PHG development. They argued that PHG should be treated by reducing portal pressure rather than reversing the hyperdynamic circulation^[155,156].

Glucagon: Glucagon levels are elevated in patients with portal hypertension^[118]. Curvêlo *et al.*^[54] found in 43 patients with PHG from portal hypertension with cirrhosis, that the mean serum glucagon level after an overnight fast was significantly higher than the level in healthy controls. Serum glucagon levels were significantly correlated with high systemic vascular resistance index (*r* = -0.523; *P* = 0) and HVPG (*r* = 0.34; *P* = 0.019). Glucagon significantly increases portal pressure^[157-159], and causes splanchnic vasodilation^[148]. Geraghty *et al.*^[158] found a strong correlation between portal pressure and glucagon levels (*r* = 0.85). Tsui *et al.*^[160] reported that glucagon significantly increased portal pressure in rats with portal vein ligation, but did not alter portal pressure in sham-operated rats. The effect of glucagon occurred only in rats with preexisting portal hypertension. Exogenous glucagon rendered gastric mucosa more susceptible to injury from toxins, such as ethanol, which was attenuated by somatostatin^[160]. For example, the lesion area was significantly higher at > 60% of gastric mucosa after glucagon administration, compared to somatostatin or glucagon and somatostatin administration (*P* < 0.05, ANOVA)^[160].

Prostaglandins: Studies in patients or animal models with portal hypertension failed to show significant differences in prostaglandin E2 (PGE2) levels as compared to healthy controls^[125,141,161-163]. Low prostaglandin levels significantly decreased gastric perfusion velocity in cirrhotic rats, whereas misoprostol, a PGE2 analogue, significantly increased gastric perfusion in cirrhotic rats as compared to controls^[125]. For example, Beck *et al.*^[125] found that administration of indomethacin did not affect gastric perfusion velocity in healthy control rats, despite reducing gastric PGE2 synthesis by > 95%, but reduced gastric perfusion velocity by 30% within 10 min in cirrhotic rats achieved by ligating the common bile duct (*P* < 0.05). The hyperemic response to application of ethanol was significantly reduced in cirrhotic rats compared to healthy rats (56.3% ± 21.7% (SD) vs 66.1% ± 17.1% (SD) increase, *P* < 0.05). Misoprostol applied to gastric mucosa caused

concentration-dependent increase in perfusion velocity, with a significantly greater increase in perfusion velocity in cirrhotic rats with concentrations of misoprostol > 0.8 mcg/mL ($P < 0.05$).

Beck *et al.*^[164] further reported that administration of misoprostol to cirrhotic rats for 1 mo restored the hyperemia in response to ethanol that sham-operated, non-cirrhotic rats showed, whereas placebo-treated cirrhotic rats failed to increase gastric blood flow in response to ethanol. PGE2-treated cirrhotic rats exhibited significantly less spontaneous gastric mucosal damage [$0.2\% \pm 0.07\%$ (SD)] than placebo-treated cirrhotic rats [$3.0\% \pm 0.8\%$ (SD); $P < 0.05$]. The mean microscopic gastric injury score was significantly less in PGE2-treated cirrhotic rats [0.7 ± 0.3 (SD)] than in placebo-treated cirrhotic rats [2.1 ± 0.4 (SD); $P < 0.05$].

Rats with PHG exhibited suppression of gastric mucosal COX-1 levels, but exhibited normal COX-2 levels compared to healthy controls^[141]. Nonselective COX inhibitors, such as aspirin, decrease PGE2 levels resulting in more apoptosis of cells. Payen *et al.*^[123] reported that gastric mucosal potential difference, an index of mucosal integrity, decreased with increasing severity of PHG, suggesting greater vulnerability of gastric mucosa in patients with PHG. Payen *et al.*^[123] further reported a significantly greater decline of potential difference after aspirin administration of 11.1 ± 3.6 (SD) mV in 9 patients with severe PHG, vs 9.2 ± 3.6 mV in 21 patients with moderate PHG ($P < 0.05$), and vs 6.4 ± 1.9 (SD) mV in 10 healthy controls ($P < 0.05$). Also, PGE2 administration suppressed the increased apoptosis which occurred in rats with PHG.

Prostacyclin: Prostacyclin, a vasodilator that inhibits gastric acid secretion, has been proposed as a mediator of the hyperdynamic circulation in PHG from portal hypertension^[148,163]. Ohta *et al.*^[161] found significantly elevated serum levels of 6-keto-PGF_{1 α} , a metabolite of prostacyclin, in cirrhotic patients with PHG. They also reported that these patients had significantly elevated levels of 6-keto-PGF_{1 α} in the mucosa of the gastric fundus.

Other cytokines and growth factors: Several studies have analyzed the roles of endothelin-1, VEGF, and other cytokines in PHG, but further research is required^[165]. The gastric concentrations of epidermal growth factor were comparable between patients with and without PHG, and its significance in PHG remains unclear^[166]. A high serum level of autotaxin, involved in liver fibrosis, was associated with advanced stage of cirrhosis, presence of esophageal varices, and PHG^[167].

Helicobacter pylori: Numerous studies demonstrated that *Helicobacter pylori* (*H. pylori*) infection is not associated with PHG^[7,9,25,79,109,110,154,168-172]. Indeed, several studies reported that patients with PHG less frequently have *H. pylori* infection than controls. *H. pylori* does not appear to play a pathogenic role in

ulcers associated with PHG^[173]. Contrariwise, Sathar *et al.*^[174] reported an association between *H. pylori* infection and PHG in cirrhotic patients, but this study apparently had limitations, including low specificity and low sensitivity of *H. pylori* serology in cirrhotic patients, potential selection bias, and underreporting of *H. pylori* seroprevalence^[174-178].

Diagnosis

Endoscopy: PHG is diagnosed by EGD^[72]. The characteristic endoscopic appearance is a mosaic-like pattern or a diffuse, erythematous and reticular cobblestone pattern of gastric mucosa consisting of small polygonal areas, with superimposed red punctate lesions, > 2 mm in diameter and a depressed white border^[78,96,177]. The red lesions vary in size and in color depending on PHG severity. The lesions range from pink speckled lesions within a mosaic or snakeskin pattern in mild cases, to localized small areas of intense erythema, resembling a scarlatina rash, in severe cases^[70,71,112,139]. These findings occur predominantly in the gastric body and fundus, and rarely in the antrum^[71,72,139]. Figure 2 illustrates a patient with classic endoscopic findings of portal hypertensive gastropathy. Toyonaga *et al.*^[178] reported in a meta-analysis of 6 studies that the mosaic-like pattern had high specificity at 98% (range: 93%-100%), but low sensitivity at 38% (range: 7%-94%) for PHG, with an accuracy of 78% (range: 63%-98%). In severe PHG numerous petechiae and bleeding spots present as a diffuse hemorrhagic gastropathy^[112,139].

Endoscopic classification: Endoscopic classification of PHG severity is clinically important because severity is correlated with bleeding risk^[31,71,72,179]. PHG can be simply categorized as mild with a mosaic-like pattern without red spots, or as severe, with superimposed red lesions present^[78,96]. Multiple formal endoscopic classifications exist (Table 8^[3,7,8,70,180-183]), with no consensus as to which classification is the best^[5,182-184]. The following classifications are commonly used: Classifications by McCormack *et al.*^[3], Tanoue *et al.*^[180], the New Italian Endoscopic Classification (NIEC)^[70], and the Baveno scoring system^[181].

In 1985, McCormack *et al.*^[3] classified PHG according to presence of red spots into mild and severe disease. In 1991, McCormick *et al.*^[7] divided the prior single category of mild PHG into mild and moderate PHG based on absence vs presence of erythema, respectively. This moderate category is infrequently used^[7]. In 1992 Tanoue *et al.*^[180] and Parker *et al.*^[185] also expanded the scoring system by providing a grade between mild and severe. This classification is rendered cumbersome by a lack of sharply defined differences between the added intermediate category and the original categories^[71]. This system is, however, simple and can help predict bleeding risk^[71,182]. Iwao *et al.*^[186] found McCormack's classification was accurate for fine pink speckling in 54%, for snakeskin pattern in 76%, and for cherry-red spots in 64%. The NIEC produced a better definition in



Figure 2 A 60-year-old man presented for routine endoscopic screening for esophageal varices due to a history of Child-Pugh class B cirrhosis, with a model for end-stage liver disease score = 18, from hepatitis C secondary to former intravenous drug use. The patient denied a history of gastrointestinal bleeding. The hematocrit was 40.1%. Esophagogastroduodenoscopy revealed the classic findings of portal hypertensive gastropathy, including a pale white reticular (mosaic) pattern surrounding small polygonal areas of mucosa, with variable erythema, in the entire stomach, but most prominently in the gastric fundus and body. B is a relatively close-up view of the lesions seen in A.

Table 8 Different classification systems for portal hypertensive gastropathy

Ref.	Mild	Moderate	Severe
McCormack <i>et al</i> ^[31]	Fine pink speckling (scarlatina type rash) Superficial reddening, especially on rugal surface (striped appearance) Fine white reticular pattern separating areas of raised edematous mucosa (snake skin)		Discrete red spots (analogous to cherry red spots in esophagus) Diffuse hemorrhagic gastritis
McCormick <i>et al</i> ^[71] Tanoue <i>et al</i> ^[180]	Mosaic or snake skin appearance Mild reddening, congestive mucosa, no mosaic-like pattern	Presence of erythema Severe redness and a fine reticular pattern separating the areas of raised edematous mucosa (mosaic-like pattern) or a fine speckling	Presence of erosions or hemorrhagic gastritis Grade III (severe) Point bleeding + grade II (moderate)
Spina <i>et al</i> ^[70] (NIEC)	Mosaic-pattern: Presence of small, polygonal areas surrounded by a whitish-yellow depressed border		Red point lesions (1 mm in diameter, flat) Cherry-red spots (2 mm, slight protrusion) Black-brown spots (irregularly shaped, persistently present after washing)
Sarin <i>et al</i> ^[81]	Discrete cherry red spots, with or without mosaic pattern		Presence of confluent red spots, diffusely distributed in a large portion of the stomach
Sarin <i>et al</i> ^[181] (Baveno II Consensus Workshop) ^[181]	Mild ≤ 3 points ¹		Severe ≥ 4 points ¹ Gastric antral ectasia Absent (0) Present (2)
Yoo <i>et al</i> ^[182] 2-category classification	Fine pink speckling (scarlatina type rash) Superficial reddening Mosaic pattern		Discrete red spots Diffuse hemorrhagic lesion
Yoo <i>et al</i> ^[182] 3-category classification	Mild reddening Congestive mucosa Diffuse pink areola	Flat red spot in center of a pink areola Severe redness and a fine reticular pattern	Diffusely red areola Pinpoint bleeding Discrete or confluent red mark lesion

¹Points assigned for Baveno II consensus according to the following: Mild mucosal mosaic pattern = 1 point, severe mucosal mosaic pattern = 2 points; isolated red markings = 1 point, confluent red markings = 2 points; gastric antral ectasia present = 2 points.

1992 of mild and severe HPG^[32,34,70]. Elementary lesions of PHG according to the NIEC classification include: (1) mosaic-like pattern defined as small, polygonal areas surrounded by a whitish-yellow, depressed border. This mosaic pattern is mild when the areola is uniformly pink, moderate if the center is red, and severe if the areola is uniformly red; (2) red-point lesions defined as small, flat, 1-mm-wide, punctate, red lesions; (3) cherry-red spots defined as red, 2-mm-wide, round lesions which protrude slightly into the gastric lumen;

and (4) black-brown spots defined as irregularly shaped flat black or brown spots from intramucosal hemorrhage that remain after endoscopic irrigation. PHG is defined as mild when only a mosaic-like pattern of any degree was present, and severe when red-point lesions, cherry red spots, or black-brown spots were present. Due to variable data on the classification systems, Hashizume *et al*^[184] proposed a simplified classification that divides PHG into three stages by presence of: Non-specific redness, a mosaic pattern, and red spots.

Yoo *et al.*^[182] demonstrated substantial limitations in intra-observer and inter-observer reproducibility in the most common 2-scoring and 3-scoring systems. Nevertheless, the 2-scoring system by McCormack *et al.*^[3,7] produced better and more reproducible results than the 3-scoring system by Tanoue *et al.*^[180]. The mean inter-observer kappa value was 32% higher and mean intra-observer kappa value was 15% higher for the 2-scoring system compared with the 3-scoring system. However, both inter-observer and intra-observer kappa values in both classification systems were below the desirable value of > 0.75 ^[187]. Kappa values represent the degree of agreement as compared with that expected by chance alone, with one being perfect agreement, and zero being no greater agreement than expected by chance alone^[182].

The Baveno scoring system uses point calculations to define PHG as mild (≤ 3 points) vs severe (≥ 4 points)^[181]. This system adds gastric antral vascular ectasia (GAVE) into the classification^[179]. Stewart *et al.*^[179] showed that this scoring system was reproducible and accurately reflected the risk of PHG-related bleeding in cirrhotic patients. Kappa values for mucosal mosaic pattern, red marks, and GAVE were > 0.75 , indicating good reproducibility. Kappa values for lesion severity were lower, attributed to loss of details in endoscopic photographs.

de Macedo *et al.*^[187] proposed analyzing binary criteria such as presence vs absence of mosaic-like pattern, red punctate lesions, and cherry-red spots, without subdivisions or classification systems. These binary criteria were associated with high inter-observer reliability and accuracy (94%, 81% and 83% respectively). Mosaic-like pattern was associated with high sensitivity (100%). The previously used classifications and subdivisions showed unsatisfactory reliability and low inter-observer agreement.

Current classification systems are suboptimal. The ideal classification system should be simple, clinically useful, accurate, and reproducible with high levels of intra-observer and inter-observer agreement^[183]. The 2-scoring system is most commonly used due to relative simplicity and reasonable reproducibility^[71].

Capsule endoscopy: Several studies evaluated the diagnostic accuracy of capsule endoscopy. In a study using the PillCam ESO capsule, capsule endoscopy had an overall concordance with EGD of 90.6% for PHG^[188]. This study included only 32 patients of whom 19 had PHG, and a large trial is underway to confirm these findings. In another study, PHG was identified by capsule endoscopy in 13 (68.4%) of 19 patients with cirrhosis, portal hypertension, and chronic anemia, but the 19 patients did not undergo EGD to determine capsule endoscopy test sensitivity and specificity^[49]. In a study of 50 patients with cirrhosis undergoing both EGD and capsule endoscopy for screening or surveillance of esophageal varices, capsule endoscopy had an accuracy of 57%, sensitivity of 96%, and specificity of

17% compared to EGD. Inter-observer reliability was 0.61. The researchers concluded that more data are required to assess accuracy of capsule endoscopy for diagnosis and staging of PHG^[52]. In another study of 50 patients with portal hypertension undergoing EGD and capsule endoscopy, only 24 of 35 patients with PHG diagnosed by EGD had PHG detected by capsule endoscopy (sensitivity = 69%)^[23]. Capsule endoscopy was somewhat more sensitive at detecting severe than mild PHG (82% vs 63%), but this difference was not significant ($P = 0.44$). The accuracy was significantly higher in diagnosing PHG in the gastric body (100%) than the fundus (48%) ($P = 0.0009$).

Dynamic CT: Kim *et al.*^[50] proposed using dynamic CT to diagnose PHG by demonstrating the transient perfusion defect sign, defined as the presence of transient segmental or subsegmental hypo-attenuating mucosa in the gastric fundus or body during hepatic arterial imaging that returns to normal attenuation on portal venous or equilibrium-phase imaging. This sign had a sensitivity of 75%, specificity of 88.6%, positive predictive value of 90%, and negative predictive value of 72.1% for diagnosing PHG in patients with cirrhosis. Further prospective trials are required to validate this diagnostic modality.

Screening for PHG is currently not recommended in patients with liver disease^[189]. To identify predictors of PHG and varices noninvasively in patients with chronic liver disease to increase the cost-benefits of EGD, Min *et al.*^[190] combined three independent parameters in a multivariate analysis into a "Varices and PHG" (VAP) score. The score = platelets/mm³ \times albumin in g/dL/multidimensional index for spleen volume (M-Index) in cm³. The M-Index is calculated from spleen length, width, and thickness, as determined by helical computerized tomography, which is designed to reflect splenomegaly as a predictor of esophageal varices and PHG. A VAP cut-off value of 861 had a sensitivity of 85%, positive likelihood ratio of 3.17, and negative predictive value of 86%. This scoring system requires prospective validation^[190].

Differentiation from GAVE: Differentiation of PHG from GAVE is important because they have distinct pathologic, clinical, and endoscopic characteristics, and different therapies (Table 9)^[34,37,71,72,75,77,103,106,191-213]. Treatments that reduce portal pressure are effective for PHG but ineffective for GAVE^[193]. PHG and GAVE also affect different gastric locations. PHG generally affects the proximal stomach, whereas GAVE generally affects the distal stomach^[139]. A mosaic-like pattern surrounding polygonal areas of erythema is typical for PHG, but GAVE has erythema most commonly arranged linearly along folds in the antrum, less commonly arranged as diffuse erythema in the antrum, and least commonly arranged as diffuse gastric erythema^[75,78,96].

PHG is usually diagnosed by endoscopic criteria. When endoscopic features are uncertain, histologic

Table 9 Differences between portal hypertensive gastropathy and gastric antral vascular ectasia

Parameter	Portal hypertensive gastropathy	Gastric antral vascular ectasia	Ref.
Associated conditions	Conditions associated with portal hypertension: cirrhotic or non-cirrhotic portal hypertension	Cirrhosis, autoimmune disorders, and connective tissue diseases (scleroderma, pernicious anemia, hypothyroidism)	[72]
Association with portal hypertension	Strong association	Only 30% of cases	[191,192]
Sex	Mildly more common in males (alcoholic cirrhosis more common in males than females)	Much more common in females (80%)	[193,194]
Age	Can occur at any age in patients with portal hypertension or cirrhosis	Typically elderly (average age > 70 years old)	
Location	Proximal stomach: Fundus, body	Distal stomach: Antrum	[72,192]
Diagnosis	Endoscopy (endoscopic biopsy sometimes useful). Radiologic imaging usually not helpful	Endoscopy (endoscopic biopsy sometimes useful)	[72,195]
Appearance at endoscopy	Mosaic/snakeskin mucosa with red or brown spots	Tortuous columns of ectatic vessels in "watermelon" or diffuse pattern; erythematous or hemorrhagic	[191]
Histology	Ectatic capillaries, mildly dilated mucosal and submucosal veins; no vascular inflammation, no vascular thrombi	Marked dilation of capillaries and venules in gastric mucosa and submucosa with areas of intimal thickening, fibrin thrombi, fibromuscular hyperplasia and spindle cell proliferation	[72,191,196,197]
Clinical presentation/ complications	Gastrointestinal bleeding: Usually chronic, but sometimes acute	Almost exclusively chronic gastrointestinal bleeding with guaiac positive stools	[37,193]
Primary prophylaxis	Not indicated	Not indicated (unless associated with large varices)	[198]
Medical therapy	Non-selective β -adrenergic receptor antagonists (propranolol), octreotide (for acute bleeding)	No benefit of β -adrenergic receptor antagonists Oral contraceptive pills to temporarily control bleeding Questionable benefit of octreotide	[103,106,198-201]
Endoscopic therapy	Occasionally helpful (for focal bleeding) Argon plasma coagulation Local hemostasis with hemospray	Very helpful at reducing risk of bleeding: Argon plasma coagulation; EBL; Radiofrequency ablation; YAG laser therapy	[202-207]
TIPS	Significantly reduces severity and risk of bleeding by reducing portal hypertension. Option for very severe bleeding from PHG or for moderate PHG in patients with variceal bleeding	Not recommended. Does not affect severity of GAVE or risk of bleeding	[75,77]
Liver transplantation	Resolves. Ultimate therapy mostly reserved for patients with end-stage liver disease	Improves or resolves with liver transplantation	[75,200,208-210]
Other surgery	Usually resolves with shunt surgery that lowers portal pressure. Partial gastrectomy not recommended	Limited surgical resection (partial gastrectomy) recommended for refractory cases. Shunt surgery not recommended	[75,200,211-213]
Prognosis from bleeding	Bleeding rarely severe and very rarely fatal	Bleeding occasionally severe	[34,71,72]

YAG: Yttrium aluminum garnet; TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy; GAVE: Gastric antral vascular ectasia; EBL: Endoscopic band ligation.

analysis of gastric biopsies is useful to differentiate PHG from GAVE^[86,183,197,212]. Superficial mucosal biopsies are frequently falsely negative because the lesions of PHG are generally submucosal^[214,215]. Endoscopists are reluctant to perform deep biopsies in patients with known portal hypertension or suspected PHG because of increased risks of bleeding because of a coagulopathy from underlying cirrhosis or a bleeding diathesis from underlying portal hypertension^[137,183]. However, deep biopsies may be necessary for the histologic diagnosis of PHG.

Characteristic histologic findings of PHG include capillary and venule dilatation, and markedly congested and tortuous submucosal venules^[137]. Stromal fibrosis and edema of lamina propria can occur^[137]. Inflammatory cells and fibrin thrombi are generally absent^[3,139]. Characteristic histologic features of GAVE include presence of fibrin thrombi in dilated capillaries and fibromuscular proliferation within the lamina propria^[96,216].

Differentiating GI bleeding from varices vs PHG:

PHG may occasionally resemble gastric varices at EGD. PHG can be prominent on gastric rugae in the gastric body and fundus. The intraluminal linear projections of gastric rugae might superficially resemble that of gastric varices. However, gastric varices tend to be more serpiginous than linear and tend to be grayish due to the presence of deoxygenated venous blood within varices, whereas the lesions of PHG on gastric rugae tend to be erythematous and surrounded by a prominent mosaic pattern. It is also important to distinguish between GI bleeding from esophageal varices vs PHG in patients having both lesions. Table 10 outlines differences in GI bleeding from PGH vs esophageal varices.

Clinical presentation

Acute GI bleeding: GI bleeding is the only known clinically relevant complication of PHG. PHG is responsible for < 1% of upper GI bleeding in the general population, and for about 8% of non-variceal upper GI bleeding in patients with liver disease^[217]. The reported frequency of acute upper GI bleeding in patients with

Table 10 Differences in gastrointestinal bleeding from portal hypertensive gastropathy vs esophageal varices

Parameter	Portal hypertensive gastropathy	Esophageal varices
Etiology	Portal hypertension: Cirrhotic or non-cirrhotic	Portal hypertension: Cirrhotic or non-cirrhotic
Concurrence	Frequently occur simultaneously with esophageal varices because the two diseases share common risk factors	Frequently occurs simultaneously with PHG because the two diseases have common risk factors
Location	Stomach: Predominantly fundus and body	Distal esophagus: Also can have gastric varices or ectopic varices in other gastrointestinal regions, particularly duodenum
Diagnosis	Esophagogastroduodenoscopy	Esophagogastroduodenoscopy
Endoscopic appearance	Erythematous small polygonal areas of mucosa surrounded by a fine, whitish, reticular or mosaic/snakeskin mucosa with red or brown spots	Serpiginous mucosal greyish luminal projections in distal esophagus
Clinical presentation	Mild acute or chronic bleeding	Acute gastrointestinal bleeding-typically massive
Severity of bleeding	Typically mild and not life-threatening	Typically severe and life-threatening
Histology		Not biopsied at endoscopy
Endoscopic therapy	Limited role	Variceal ligation recommended as initial therapy. Sclerotherapy an alternative therapy
Medical therapy	Octreotide Propranolol Vasopressin or vasopressin analogues-infrequently recommended any more	Octreotide Propranolol Vasopressin or vasopressin analogues-infrequently recommended any more
Blakemore tube	Not recommended	Sometimes used for refractory bleeding especially as a temporizing measure before performing more definitive therapy
Angiographic therapy	TIPS used as a last resort	TIPS recommended if endoscopic therapy fails
Transfusion of packed erythrocytes	Transfuse only to hematocrit of about 28. Over-transfusion may increase portal pressure and induce greater bleeding	Transfuse only to hematocrit of about 28. Over-transfusion may increase portal pressure and induce greater bleeding
Liver transplantation	Improves or resolves with liver transplantation	Improves or resolves with liver transplantation
Prognosis	Rarely fatal	Frequently fatal

TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy.

PHG ranges in incidence from 2%-20% (Table 11^[3,8,25,34,37,103,217,218]). Primignani *et al*^[34] reported acute GI bleeding in 2.7% of patients with PHG, whereas Stewart *et al*^[179] reported a 20% incidence of acute bleeding in patients with PHG. McCormack *et al*^[3] reported that 29 (44.6%) of 65 patients with PHG bled from this lesion. In this study, PHG was the second most common cause of GI bleeding, after esophageal varices^[3]. The reported variability is partly due to inaccuracies in the endoscopic diagnosis of PHG and in the endoscopic diagnosis of PHG as the cause of bleeding^[71]. Diagnosis of PHG as the cause of bleeding can be challenging if a bleeding point is not visualized at EGD^[71].

Major risk factors for bleeding from PHG are increasing PHG duration, extent, and severity^[72,179]. For example, > 90% of acute bleeding occurs with severe PHG^[10,35,71,72], and < 10% of acute bleeding occurs with mild PHG^[112]. Other risk factors for bleeding from PHG include advanced cirrhosis, and prior endoscopic eradication of esophageal varices^[3,5,10,81,179,180,219]. Unlike bleeding from GAVE, acute bleeding from PHG is rarely severe, very rarely fatal, and typically requires transfusion of only one-to-two units of packed erythrocytes or less^[34,71,72,139].

Chronic bleeding: The frequency of chronic bleeding ranges from 3%-26%^[25,34,37]. Stewart *et al*^[179] reported a 6% incidence of chronic bleeding from PHG, whereas Primignani *et al*^[34] reported chronic bleeding in 11% of patients with PHG (Table 11^[3,8,25,34,37,103,217,218]).

The incidence of chronic gastrointestinal bleeding from PHG is difficult to determine precisely because of variable definitions of chronic GI bleeding^[67,68]. Common definitions include: (1) > 2 g/dL decrease in hemoglobin level during > 6 mo in patients without acute GI bleeding and not receiving NSAID therapy; (2) presence of anemia in patients with cirrhosis; and (3) positive fecal occult blood (Baveno II)^[181]. Moreover, chronic GI bleeding can be overestimated if hemoglobin decline is solely used for the diagnosis. Patients with chronic liver disease frequently have anemia without GI bleeding, from causes including alcoholism, chronic kidney disease, hypersplenism, or bone marrow suppression. No studies have objectively quantified chronic blood loss from PHG.

Chronic bleeding from PHG is usually mild to moderate but occasionally severe^[37,139]. Patients after endoscopic variceal obliteration have a higher incidence of chronic GI bleeding from PHG^[10,25,72]. Chronic GI bleeding from PHG can cause iron deficiency anemia^[220,221].

Pharmacotherapy for PHG

Current pharmacologic therapies aim to reduce portal pressure to decrease bleeding from PHG^[191,214].

β -adrenergic receptor antagonists: Nonselective β -adrenergic receptor antagonists reduce portal pressure and gastric mucosal blood flow, and thereby reduce bleeding from PHG^[103,104,132,191,222-224]. Several studies evaluated the efficacy of propranolol, a nonselective β -adrenergic receptor antagonist in primary and second-

Table 11 Rates of gastrointestinal bleeding from portal hypertensive gastropathy

Ref.	Year published	Population	Bleeding from PHG	Transfusions required
McCormack <i>et al</i> ^[83]	1985	127 patients with portal hypertension of various etiologies	29 patients out of 65 with PHG, representing 25% of the total number of bleeds from all sources; 9 episodes presenting with bleeding; 71 episodes of subsequent bleeding	2-15 units required for 60 bleeds
D'Amico <i>et al</i> ^[25]	1990	212 patients with cirrhosis; 75 being treated with sclerotherapy		
Sarin <i>et al</i> ^[8]	1992	107 patients with portal hypertension presenting with variceal bleeding, undergoing sclerotherapy	No bleeding before sclerotherapy from PHG (4/107 had PHG); 2/13 post-sclerotherapy patients who developed PHG	Average of 4 units per patient with range of 2-8 units
Pérez-Ayuso <i>et al</i> ^[103]	1991	54 cirrhotic patients with PHG, in a RCT to look for rebleeding; propranolol 26 vs control 28	First hemorrhage: Acute/chronic bleeding in propranolol group 12/14; in control 12/16, rebleeding: Acute/chronic; in propranolol 6/6; in control 10/12	
Gostout <i>et al</i> ^[27]	1993	Patients admitted for GI bleeding (1496)	12 patients (0.8%), representing 8% of nonvariceal bleeding in patients with liver disease	
Primignani <i>et al</i> ^[34]	2000	373 patients with cirrhosis; PHG in 299 patients (80.1%)	8 PHG patients with acute bleeding; chronic bleeding in 34 patients	
Merli <i>et al</i> ^[37]	2004	222 cirrhotic patients with portal hypertension; 48 patients with PHG on enrollment	During follow up for 47 ± 28 (SD) mo, acute bleeding 9, chronic bleeding 7 from PHG	
Kimura <i>et al</i> ^[218]	2014	297 patients with living donor liver transplantation; retrospective analysis	2 patients bled from PHG within 3 mo after transplantation	

PHG: Portal hypertensive gastropathy; RCT: Randomized controlled trial; GI: Gastrointestinal.

dary prevention of bleeding from PHG^[104,225]. Pérez-Ayuso *et al*^[103] reported in a multi-center, randomized, controlled trial of 57 patients with acute or chronic bleeding from severe PHG with cirrhosis that the 26 patients administered propranolol at 20-160 mg twice daily rebled significantly less frequently than the 31 controls receiving only iron therapy as needed at 12 mo (38% vs 65%; $P < 0.05$), and at 30 mo follow-up (7% vs 52%, $P < 0.05$). Patients receiving propranolol were transfused less units of packed erythrocytes than the controls, but this difference was not statistically significant [0.10 ± 0.06 (SD) units/mo vs 0.60 ± 0.20 (SD) units/mo, $P = 0.08$].

Propranolol also reduced the risk of developing PHG after esophageal variceal eradication^[81]. Lo *et al*^[81] reported in a randomized, controlled trial that 40 patients receiving placebo had a significant increase in PHG severity after variceal ligation ($P < 0.01$, ANOVA), but the 37 patients receiving propranolol [mean dose = 96 ± 20 (SD) mg/d] had no significant increase in PHG severity. The frequency of PHG 6 mo after variceal ligation was significantly less in patients receiving propranolol than in the controls (48% vs 85%, $P = 0.002$). This difference gradually decreased over time and became not significant at 12 mo. Also, the mean PHG severity score was lower in patients receiving propranolol than in the controls at 6 mo after variceal ligation ($P < 0.05$).

Propranolol at 240-480 mg/d has been used to arrest acute bleeding from PHG. Bleeding stopped within 3 d in 13 (93%) of 14 patients with portal hypertension administered propranolol in one study^[101]. None of these patients rebled while receiving propranolol during a median of 23 mo of follow-up, but 4 out of 7 patients rebled after electively discontinuing propranolol therapy^[104]. Nonresponse to β -adrenergic receptor antagonists, defined as continued bleeding despite

this therapy and transfusion-dependency despite iron replacement therapy, should prompt consideration of interventional therapies^[214].

Nonspecific β -adrenergic receptor antagonists are a first line therapy for secondary prophylaxis of PHG bleeding^[191,208]. Nadolol alone was as effective as nadolol with isosorbide mononitrate in preventing the first episode of PHG bleeding^[226]. No studies have analyzed the efficacy of carvedilol, another nonspecific β -adrenergic receptor antagonist, in controlling bleeding from PHG^[227].

Somatostatin and octreotide: Somatostatin and octreotide, a synthetic somatostatin analogue, cause splanchnic vasoconstriction, reduce portal pressure, reduce portal blood flow, and decrease gastric perfusion in animal models and in patients with PHG^[105,106,160,228-231]. For example, Chan *et al*^[228] found octreotide infusion, compared to placebo, significantly increased systemic vascular resistance [3.4 ± 0.2 (SD) mmHg/mL per minute per 100 g vs 2.7 ± 0.2 (SD) mmHg/mL per minute per 100 g, $P < 0.05$], and significantly decreased portal pressure [9.9 ± 0.5 (SD) mmHg vs 12.5 ± 1.2 (SD) mmHg, $P < 0.05$] in cirrhotic rats. Another study found that somatostatin only modestly reduced portal pressure in PHG^[232]. Octreotide treatment also significantly reduced mean cross-sectional area of gastric mucosal vessels compared to placebo [1810 ± 101 (SD) microns vs 2290 ± 145 (SD) microns, $P < 0.05$], and significantly inhibited release of several vasoactive gastrointestinal polypeptides, gastric acid, and pepsinogen^[106,233]. In the stomach, somatostatin activates K^+ -ATP channels (adenosine triphosphate-dependent potassium channels) which normally protect against gastric mucosal injury in the presence of portal hypertension, and antagonizes

the portal hypertensive and injury-promoting effects of glucagon^[160].

Octreotide is a first-line treatment for acute bleeding from PHG. In a randomized controlled trial, octreotide, at 100 mcg bolus followed by infusion of 25 mcg/min for the first 24 h and then 20 mcg/min for the second 24 h, controlled bleeding from PHG in 20 (83%) of 24 patients at 24 h and in 24 (100%) of 24 patients at 48 h^[106]. Octreotide significantly more frequently controlled the bleeding than vasopressin (64%, $P < 0.005$), or omeprazole (59%, $P < 0.005$), and tended to be more effective than both vasopressin and omeprazole (88%, NS)^[106]. Octreotide also controlled the bleeding significantly faster and required significantly less transfusions of packed erythrocytes than vasopressin or omeprazole^[106]. Octreotide even successfully stopped bleeding within 48 h in the patients with bleeding refractory to vasopressin and omeprazole therapy.

Kouroumalis *et al.*^[105] reported that somatostatin or octreotide infusion for 3 d stopped severe bleeding from PHG in all 26 study patients. Only 3 patients experienced recurrent bleeding which stopped after retreatment with somatostatin, and only one patient required gastrectomy for refractory bleeding.

Somatostatin and octreotide only temporarily reduce portal pressure. Escorsell *et al.*^[232] reported rapid desensitization to the effects of octreotide with prolonged administration in cirrhotic patients with portal hypertension. Therefore somatostatin and octreotide are useful for acute bleeding but not for preventing chronic bleeding from PHG. Octreotide did not significantly change the severity of PHG at endoscopy.

Vasopressin and terlipressin: Vasopressin, a systemic vasoconstrictor, reduces splanchnic blood flow, lowers portal pressure, and decreases gastric mucosal blood flow^[106]. In a randomized, controlled trial, vasopressin, administered intravenously (IV) at a rate of 1 unit/min for the first 10 min, followed by continuous infusion at 0.1 unit/min for 48 h, arrested bleeding from PHG in 14 (64%) of 22 patients^[106]. However, as aforementioned, this result was inferior to that achieved by octreotide, possibly because vasopressin does not inhibit release of peptides, including glucagon and vasoactive intestinal polypeptide, and does not inhibit gastric acid secretion^[106]. Concomitant omeprazole therapy may modestly increase vasopressin efficacy^[106]. Vasopressin is considered an alternative therapy to octreotide.

Vasopressin causes significantly more frequent side effects (41%) than octreotide, especially abdominal pain^[106]. Vasopressin reduces oxygen saturation of gastric mucosa, but this reduction can be partly reversed by administering supplemental oxygen^[234,235]. Two analogues of vasopressin have been studied. Glypressin showed similar reduction in gastric mucosal perfusion as vasopressin by laser-Doppler flowmetry, but less impairment in gastric mucosal oxygenation^[235]. Terlipressin may be useful in controlling acute bleeding from PHG,

especially when used at a dose of 1 mg IV every 4 h for 5 d^[103,107,192].

Antioxidants: Antioxidants help in free radical scavenging and in reversing impairment of oxidative stress-induced ERK2 activation. They may decrease susceptibility of PHG gastric mucosa to alcoholic injury, as demonstrated by administration of vitamin E, an antioxidant^[144]. Vitamin E reduced oxidative state, normalized MKP-1 expression, and reversed impairment of oxidative stress-induced ERK2 activation^[144]. Vitamin E helped reduce gastric injury from alcohol exposure in rats with PHG^[71].

Vitamin E administration decreased mucosal lipid peroxidation, decreased lysosomal enzymes, and increased levels of antioxidants. Kaur *et al.*^[143] administered vitamin E 240 mg subcutaneously to rats with common bile duct ligation vs sham surgery. Seven days after ligation or sham surgery, the level of thiobarbituric acid reactive substances in gastric mucosa was significantly higher in ligated rats not receiving vitamin E [0.78 ± 0.22 (SD) nmol of malondialdehyde formed/mg protein] as compared to sham surgery rats administered vitamin E [0.56 ± 0.07 (SD) nmol of malondialdehyde formed/mg protein, $P < 0.01$]. These data suggest that vitamin E decreased mucosal lipid peroxidation. In the ligation group vitamin E administered preoperatively significantly reduced the levels of β -glucuronidase as compared to untreated or post-operatively-treated groups ($P < 0.01$). Preoperative vitamin E therapy significantly lowered levels of acid phosphatase as compared to untreated or postoperatively treated groups ($P < 0.01$). Preoperative administration of vitamin E in the ligation group led to significantly increased levels of the three major antioxidant enzymes, including superoxide dismutase ($P < 0.005$), glutathione peroxidase ($P < 0.01$), and catalase ($P < 0.05$) when compared to the levels of these antioxidant enzymes in untreated groups or in groups treated postoperatively with vitamin E. These data provide a theoretical basis that vitamin E administration may potentially improve PHG.

Kawanaka *et al.*^[144] administered vitamin E or saline for 13 d in rats with PHG vs sham-operated rats used as a control. Rats with PHG had a 2.3-fold increased area of gastric mucosal necrosis after gastric exposure to ethanol than sham-operated rats ($P < 0.05$), but vitamin E treatment in rats with PHG almost completely reversed this increased necrosis compared to controls ($P < 0.05$). Vitamin E treatment did not significantly change portal pressure or gastric mucosal blood flow in PHG gastric mucosa.

Rebamipide: Rebamipide, an antiulcer medication, protects against oxygen-derived production of free radicals by scavenging free radicals. Intra-gastric administration ameliorates oxidative stress, reduces nitration of tyrosine residues of ERK, and reverses delayed mucosal healing occurring in PHG. It reversed the increased susceptibility to ethanol-induced injury and

reversed the delayed healing after gastric injury in rats with PHG^[145]. Kinjo *et al.*^[145] reported that administration of rebamipide in rats with PHG, significantly decreased lipid peroxide and nitrotyrosine and nitration of ERK by peroxynitrite in PHG mucosa, therefore normalizing ERK activation and restoring normal gastric mucosal healing after ethanol injury. Rebamipide requires further study as a therapy for PHG^[119].

Estrogen and progesterone: Estrogen and progesterone therapy reduced gastric mucosal blood flow, portal pressure, and porto-collateral resistance in rats with surgically-induced portal hypertension^[236]. Panés *et al.*^[236] reported that treatment with estradiol, dihydroxyprogesterone, or low dose combination estradiol-dihydroxyprogesterone significantly decreased gastric mucosal blood flow in rats that underwent portal vein ligation as compared to placebo [56 ± 3.5 (SD) mL/min per 100 g for placebo; 43 ± 3.4 (SD) mL/min per 100 g for estrogen; 32 ± 2.6 mL/min per 100 g for dihydroxyprogesterone, and 42 ± 6.1 (SD) mL/min per 100 g for low dose estrogen/dihydroxyprogesterone, $P < 0.05$]. Estrogen and progesterone have not been studied in patients with PHG.

Thalidomide: Thalidomide blunts development of a hyperdynamic circulation and decreases portal pressure by reducing NO production^[114]. Thalidomide, at a low dose of 100 mg daily, was successful as a last resort therapy in one case report of bleeding from PHG caused by neoplastic invasion of the portal vein^[237]. Before thalidomide therapy, the patient had required transfusion of 30 units of packed erythrocytes during 35 d while treated with propranolol and terlipressin.

Corticosteroids: There is one case report of cessation of PHG bleeding with corticosteroid therapy, using prednisolone 20 mg/d, after being admitted for five times during 5 mo with severe iron deficiency anemia from chronic GI bleeding from PHG that was refractory to propranolol therapy. At 2 mo follow-up the hemoglobin was rising and at 4 mo follow-up repeat EGD showed an improved endoscopic appearance of PHG^[238]. The patient was stable during 3-years of follow-up using 15 mg prednisolone every other day, with no recurrence of the anemia.

Losartan: Hepatic stellate cells help modulate sinusoidal resistance and the sinusoidal microcirculation. These cells are influenced by vasoconstrictors such as endothelin and angiotensin II. The angiotensin II receptor antagonist, losartan, lowers portal pressure by inhibiting stellate cell contraction and by reducing sinusoidal resistance^[239]. Administration of losartan at 25 or 50 mg/d resulted in improvement of PHG in 9 (56.3%) of 16 patients during 4 wk of follow-up. The higher dose had greater efficacy. There was also evidence of decreased portal pressure. Further studies are needed to evaluate the effect of losartan on PHG^[239].

Sucralfate and acid-suppressing medications:

Proton pump inhibitors, sucralfate^[74], and histamine-2 receptor antagonists are not very effective at reducing bleeding from PHG because most patients with PHG already have hypochlorhydria^[79,106,240-242]. However, proton pump inhibitors may indirectly stop bleeding from the stomach by raising intraluminal gastric pH and thereby stabilizing blood clots^[243,244]. Zhou *et al.*^[106] reported that omeprazole at 40 mg IV bolus every 12 h for 48 h successfully stopped bleeding in 59% of patients with PHG bleeding. Additionally, patients whose bleeding was refractory to vasopressin, benefited from omeprazole co-administration and vice versa.

Tepranone: In a controlled clinical trial, tepranone (geranylgeranyl acetone) administered to 15 patients with PHG decreased VEGF and hexosamine content in the gastric antrum, and thereby significantly decreased the severity of PHG^[136]. Among these 15 treated patients, one patient decreased from severe to moderate PHG and another patient decreased from moderate to mild PHG^[180]. Contrariwise, all 15 patients receiving placebo experienced no change in PHG severity.

Endoscopic therapies: Endoscopic therapies play a minor role in PHG bleeding because the bleeding is typically diffuse and obscure. Little data exist on efficacy of endoscopic therapy for PHG bleeding^[71,245]. No single predominant site of bleeding is identified that can be locally treated at endoscopy. The role of endoscopic therapy is limited to the rare circumstances in which a single active bleeding site identified that is amenable to point therapy such as cauterization or sclerotherapy.

Argon plasma coagulation (APC) or hemospray, a rapid hemostatic agent, are experimental endoscopic therapies for PHG. These therapies can treat a larger bleeding surface area than cauterization or sclerotherapy. Nine (81%) of 11 patients undergoing APC for PHG bleeding achieved hemostasis, with a significant rise in hematocrit from baseline values after a mean of 2.2 ± 2.0 (SD) endoscopic therapy sessions. The other two treated patients required fewer blood transfusions after APC therapy^[202].

Hemospray has recently shown promise in halting active PHG bleeding while long-term therapy is being initiated^[203,246]. Ibrahim *et al.*^[246] reported complete cessation of diffuse bleeding from severe PHG after spraying hemospray TC-325 (a nanopowder hemostatic agent^[247]) in a 41-year-old woman who presented with a hemoglobin of 8.8 g/dL. No active bleeding was seen on follow-up endoscopy performed 24 h later. In another study, however, one of four patients treated with hemospray for bleeding from PHG expired from GI perforation^[203].

Endoscopic cryotherapy has been used for PHG bleeding after all other modalities failed. In one patient salvage cryotherapy was successful after failed TIPS and APC, with normal hemoglobin levels maintained during 4 wk of follow-up^[248].

TIPS: TIPS increases gastric mucosal blood flow while decreasing total gastric blood flow due to decreasing portal hypertension^[76]. TIPS reduces the frequency and severity of PHG because it lowers portal pressure^[76]. PHG can sometimes resolve completely after TIPS^[75-77,249-253]. Urata *et al*^[77] reported in a prospective study of 12 Japanese patients undergoing TIPS for portal hypertension that portal pressure declined from 25.1 ± 8.8 (SD) mmHg before TIPS to 17.1 ± 6.2 (SD) mmHg after TIPS ($P < 0.005$). This decline in portal pressure was correlated with a significant decrease in PHG severity after TIPS ($P < 0.01$), and a significant decrease in number of patients with PHG (10 before vs 4 after TIPS, $P < 0.01$). In particular, PHG disappeared in 2 of 5 patients who had severe PHG before TIPS. Mezawa *et al*^[76], likewise, reported that mean portal pressure declined from 23.4 to 14.0 mmHg in 16 cirrhotic patients after TIPS ($P < 0.01$). All four patients with severe PHG before TIPS, had significant improvement in PHG severity after lowering portal pressure with TIPS, and five of 12 patients with mild PHG had resolution of PHG after TIPS. In contrast, GAVE does not resolve after lowering portal pressure with TIPS, and GAVE is, therefore, likely related to hepatic dysfunction rather than portal hypertension^[78].

TIPS also decreased the risk of PHG bleeding^[75-77,100,249-253]. For example, Kamath *et al*^[75] reported TIPS led to improvement or resolution of PHG findings and decreased transfusion requirements from 2.9 ± 2.0 (SD) units/mo of packed erythrocytes before TIPS to 0.6 ± 0.8 units/mo after TIPS performed for severe PHG ($P = 0.04$). Ashraf *et al*^[98] reported one patient with chronic liver disease from hepatitis C who presented with chronic bleeding from PHG that required transfusions of 28 units of packed erythrocytes during the prior 6 mo. The bleeding ceased after TIPS with marked improvement in the severity of PHG. Contrariwise, GAVE does not respond to TIPS or other measures that lower portal pressure.

Shunt surgery: Shunt surgery decreases portal hypertension, decreases PHG severity, decreases risk of PHG bleeding, and may sometimes completely resolve the endoscopic features of PHG^[100]. Shunt surgery is rarely used today to control bleeding because TIPS is preferred because of less invasiveness^[100,101,238,254].

TIPS and shunt surgery are therapies of last resort for patients who fail other therapies for PHG because they entail more morbidity and mortality than pharmacologic therapy^[71]. TIPS, however, is very useful for refractory bleeding from esophageal varices from portal hypertension^[255], and is a reasonable option in patients having recurrent severe bleeding from PHG despite administration of β -adrenergic receptor antagonists^[102].

Other invasive therapies: Liver transplantation is the ultimate therapy for PHG^[118]. In a study of 29 patients undergoing living donor liver transplantation for end stage liver disease, PHG resolved in all 19 patients who

had PHG before transplantation^[44].

Kimura *et al*^[218] retrospectively examined the 19 patients experiencing gross GI bleeding, defined as gross melena or hematemesis, within 3 mo after liver transplantation among 297 patients undergoing living donor liver transplantation. The etiologies included PHG in 2 patients, varices in 1, anastomotic ulcer in 13, and other in 3.

Splenic embolization, by transcatheter splenic arterial embolization, significantly improves PHG in patients with hypersplenism as compared to controls^[99,255]. Ohmagari *et al*^[99] evaluated 30 patients with hypersplenism who underwent transcatheter splenic arterial embolization in 17 vs no interventional therapy in 13 patients. Splenic embolization significantly reduced the frequency of PHG (reduction of 71% vs 8%, $P < 0.05$). Partial splenic embolization also successfully controlled PHG bleeding in one case report^[256].

Laparoscopic splenectomy, for various indications, was reported to decrease PHG severity^[55]. Anegawa *et al*^[55] prospectively analyzed the effect of laparoscopic splenectomy on preexistent PHG in 70 patients with liver cirrhosis from various etiologies. All patients underwent EGD before and 1 mo after splenectomy. Splenectomy was performed for indications of bleeding diathesis, interferon induction, hepatocellular cancer treatment, and sclerotherapy-resistant varices. Before splenectomy, 49 of 70 patients had PHG, including mild PHG in 32 and severe PHG in 17 patients. After splenectomy, PHG resolved completely in 7 patients with prior severe PHG, resolved completely in 12 patients with mild PHG, and was reduced from severe to mild PHG in 9 patients ($P < 0.0001$).

Summary of clinical treatment

Acute bleeding: Variceal bleeding must be excluded by performing EGD before initiating treatment for PHG^[257,258]. General measures for patients presenting with acute bleeding from PHG include volume resuscitation and cautious transfusion of packed erythrocytes, as necessary, to maintain the hemoglobin level at 8 g/dL^[192,259,260]. Over-transfusion to a higher hemoglobin level could promote bleeding from PHG by raising portal pressure, as reported for bleeding from esophageal varices^[261,262]. However, patients with cardiopulmonary disease or severe other comorbidities may require a hemoglobin level of 9-10 g/dL^[263]. Antibiotic prophylaxis is generally recommended for bleeding from PHG^[214], just as it is recommended for esophageal variceal bleeding in cirrhotic patients^[189,264-266] because of an increased risk of systemic infections, particularly spontaneous bacterial peritonitis, in cirrhotic patients with GI bleeding^[267].

Bleeding from PHG may be exacerbated by a coagulopathy with an elevated international normalized ratio from advanced liver disease. This coagulopathy may require transfusion of fresh frozen plasma. Severe thrombocytopenia may occur from bone marrow suppression in alcoholic cirrhosis and from hypersplenism with portal hypertension in any cirrhotic patient.

Table 12 Treatment of acute or chronic gastrointestinal bleeding from portal hypertensive gastropathy

Acute bleeding
Patient stabilization
Treat severe coagulopathy with highly elevated INR associated with cirrhosis with fresh frozen plasma
Treat severe thrombocytopenia associated with hypersplenism and bone marrow suppression from alcoholism with platelet transfusions
Transfuse packed erythrocytes to main hemoglobin level at about 8 g/dL
Consider antibiotic prophylaxis in patient with cirrhosis
Endoscopic therapy from bleeding-rarely used
Consider argon plasma coagulation
Hemospray - an experimental therapy
Pharmacotherapy
Octreotide - first line therapy
Vasopressin or terlipressin - second line therapy
Proton pump inhibitor therapy - adjunct therapy
Propranolol - can be instituted after bleeding controlled and patient stabilized
Interventional therapy
TIPS - for uncontrolled hemorrhage or for bleeding from PHG associated with variceal bleeding
Liver transplantation - for advanced end stage liver disease
Chronic bleeding
Treatment of anemia
Transfusions of packed erythrocytes as necessary
Iron replacement therapy
Pharmacotherapy
Consider propranolol

TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy; INR: International normalized ratio.

Platelet transfusion may be necessary for severe thrombocytopenia in the setting of active bleeding from PGH.

Somatostatin or octreotide are first line therapies. Vasopressin or terlipressin are second-line therapies for acute bleeding^[106]. Once the acute bleeding is controlled and the patient is hemodynamically stable, a nonselective β -adrenergic receptor antagonist is instituted for secondary prevention of PHG bleeding^[103,258,268]. Propranolol is the recommended drug in this class because it has been the most studied. Propranolol should be started at a dose of 20 mg twice daily and gradually escalated to 160 mg twice daily or the maximum tolerated dose, maintaining it as long as the portal hypertension is present^[214]. The dose is titrated to slow the pulse to 60 beats/min. This class of drugs is not used in the acute setting because it can blunt the physiologic tachycardia to restore end-organ perfusion in response to hypovolemia and requires gradual dose titration to achieve an adequate response^[214]. This class of drugs also prevents bleeding from concomitant esophageal varices.

Treatment of chronic bleeding: Scant data exist regarding management of chronic bleeding from PHG^[72]. In patients with suspected chronic bleeding from PHG, after excluding other etiologies, iron replacement therapy should be initiated to avoid depleting iron reserves^[260]. Propranolol is the primary therapy to reduce portal pressure and prevent chronic bleeding^[72,214,260]. However, propranolol was not superior to placebo in one study, as determined by percentage of patients free from chronic GI bleeding during long term follow-up^[103].

Liver transplantation is an option in patients with decompensated cirrhosis and PHG bleeding. Table 12 summarizes the recommendations for the treatment of

acute and chronic bleeding from PHG.

Prevention

The risk of bleeding from mild PHG is low. Primary prophylaxis is, therefore, not recommended for patients with mild PHG^[72,191,269]. Propranolol can be used for primary prophylaxis for severe PHG, and can significantly reduce the risk of bleeding. However, scant evidence exists that this reduction will affect the risk of a primary bleeding episode in PHG patients^[72,103,104,269,270]. Propranolol is recommended regardless of the severity or presence of PHG in patients with esophageal varices because it treats both entities by reducing portal pressure^[105-107,198,271,272].

Prophylaxis of bleeding from PHG is not recommended^[260]. Current guidelines do not recommend endoscopic surveillance in patients with cirrhosis who have asymptomatic PHG, without evident esophageal varices, other than the standard surveillance for development of esophageal varices in these patients^[189].

Mortality: Limited data exist on mortality from bleeding from PHG, but this bleeding is rarely fatal^[72]. It contributes little to overall morbidity and mortality from portal hypertension, especially in comparison to variceal bleeding^[118]. It represents a minor cause (< 1%) of mortality in cirrhotic patients because the bleeding is typically mild^[25,34,37,71]. Only one patient expired from PHG in one series of 38 deaths among 373 study patients with cirrhosis^[34]. Bleeding-related mortality was much lower for PHG [1 of 8 patients (12.5%)] than that for esophageal varices [9 of 20 patients (45%)]^[34].

Lesions resembling PHG in other gastrointestinal regions: PHG-like lesions can occur in other parts of

the GI tract and are named according to the involved segment as portal hypertensive duodenopathy^[40], portal hypertensive biliopathy, small intestinal vasculopathy^[139], and portal hypertensive colopathy^[96,139]. These uncommon extragastric lesions occur particularly in patients with extrahepatic portal hypertension^[71]. Portal hypertensive duodenopathy has been defined as the endoscopic appearance of patchy or diffuse congestion of duodenal mucosa associated with portal hypertension^[40], but a consensus definition is not established^[273]. Histologically, vascular changes predominate, including capillary angiogenesis, dilatation and congestion, as well as fibrous proliferation and apoptosis^[46]. This duodenopathy is significantly more severe in patients having severe than mild PHG (56.8% vs 23.5%, $P < 0.05$)^[46]. Portal congestive jejunopathy is defined histologically by the presence of ectatic capillaries and venules in the villi, with an increase in the number of vessels to $> 6/villus$ ^[274]. Portal hypertensive ileopathy^[275], and portal hypertensive colopathy^[38,276] are also associated with portal hypertension. The colopathy histologically appears as dilatation of mucosal blood vessels and is classified into four different types by Ito *et al.*^[38], including solitary vascular ectasias, diffuse vascular ectasias, erythema, and blue vein.

DISCUSSION

The pathophysiology of PHG is not well understood. Portal hypertension plays a central role in the pathogenesis, and liver disease a subsidiary role in the disease, but a hyperdynamic circulation likely also plays an important role. However, the precise nature and pathophysiology of the hyperdynamic circulation must be further elucidated. The pathophysiology of more severe gastric mucosal injury and blunted reparative response after exposure to toxic substances in PHG must be clarified in terms of molecular mediators and histopathology. In particular, the pathophysiologic basis of decreased superficial mucosal perfusion in PHG must be better characterized in terms of its molecular mechanisms.

The current pharmacotherapy for bleeding from PHG focuses on decreasing portal pressure because portal hypertension is a prerequisite for developing PHG. Understanding the molecular mechanisms of this disease may permit development of better targeted and more effective pharmacotherapies.

COMMENTS

Background

Portal hypertensive gastropathy (PHG) is characterized at endoscopy by characteristic lesions present in the proximal stomach; characterized pathophysiologically by a hyperdynamic circulation induced by portal hypertension by inadequately understood mechanisms; and characterized clinically by mild-to-moderate acute or chronic gastrointestinal bleeding from the endoscopically identified lesions. However, much about the pathophysiology and clinical therapy of PHG is inadequately understood. This work systematically reviews the literature on the pathophysiology, natural history and

therapy of PHG to report what is known and what is not known or controversial about PHG.

Research frontiers

This work systematically reviews gaps or controversies in the current understanding of PHG. First, this work exposes gaps in the current understanding of the pathophysiology. Portal hypertension is necessary but insufficient to develop PHG because many patients have portal hypertension without PHG. The pathogenesis is related to a hyperdynamic circulation, induced by portal hypertension, characterized by increased intrahepatic resistance to flow, increased splanchnic flow, increased total gastric flow, and most likely decreased gastric mucosal flow. However, this review shows that the cellular and molecular mechanisms for this hyperdynamic circulation are inadequately characterized. Nitrous oxide, free radicals, tumor necrosis factor- α , and glucagon may be important mediators of PHG. Second, this work reports the inadequacies of the current recommended therapies for PHG and for bleeding from PHG based on the currently inadequate understanding of the pathophysiology. This work should be useful to clinicians, clinical researchers, and basic researchers by describing what is known, controversial, or unknown about the pathophysiology, natural history, and therapy of PHG. It is hoped that this work stimulates further research in this field by exposing gaps in the current understanding of PHG.

Innovations and breakthroughs

This systematic review extensively reviews what is known and what is not known or controversial about PHG. This work is particularly helpful to clinicians in reporting the current recommended therapy for PHG, the clinical trials supporting the current recommendations, and the limitations of the current therapies. This is also helpful to clinical and basic researchers in systematically reviewing the current state of knowledge about its pathophysiology, including gaps, uncertainties, and controversies in the current understanding of the pathophysiology.

Applications

This systematic review extensively reviews what is known and what is not known or controversial about PHG. First, this work exposes gaps in the understanding of the pathophysiology. Portal hypertension is necessary but insufficient to develop PHG because many patients have portal hypertension without PHG. The pathogenesis is related to a hyperdynamic circulation, induced by portal hypertension, characterized by increased intrahepatic resistance to flow, increased splanchnic flow, increased total gastric flow, and most likely decreased gastric mucosal flow. However, this review shows that the cellular and molecular mechanisms for this hyperdynamic circulation are inadequately characterized. Nitrous oxide, free radicals, tumor necrosis factor- α , and glucagon may be important mediators of PHG development. Second, this work describes the natural history of PHG. PHG increases in frequency with more severe portal hypertension, advanced liver disease, longer liver disease duration, presence of esophageal varices, and endoscopic variceal obliteration. Acute and chronic gastrointestinal bleeding are the only clinical complications. Bleeding is typically mild-to-moderate. Third, this work reports the current therapies for PHG and for bleeding from PHG and characterizes their inadequacies based on the currently inadequate understanding of the pathophysiology. In particular, this work reviews clinical trials of the therapeutic efficacy of octreotide; proton pump inhibitors; nonselective β -adrenergic receptor antagonists, particularly propranolol; and vasopressin or terlipressin. This work should be useful to clinicians, clinical researchers, and basic researchers by describing what is known, controversial, and uncertain about the pathophysiology, natural history, and therapy of PHG.

Terminology

This work systematically reviews portal hypertensive gastropathy, characterized at endoscopy by characteristic lesions present in the proximal stomach; characterized pathophysiologically by a hyperdynamic circulation induced by portal hypertension by inadequately understood mechanisms, and characterized clinically by mild-to-moderate acute or chronic gastrointestinal bleeding from the endoscopically identified lesions.

Peer-review

This review by Mihajlo Gjeorgjievski on portal hypertensive gastropathy is well

written and helpful to understand its pathophysiology, clinical presentation, natural history and therapy. This review is informative and helpful to readers who are interested in the topic or subtopics.

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