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AASLD Practice Guidance on Risk Stratification and Management of Portal Hypertension and Varices in Cirrhosis

Authors: David E. Kaplan[1], Jaime Bosch[2,3]Cristina Ripoll[4], Maja Thiele[5], Brett E. Fortune[6], Douglas A. Simonetto[7], Guadalupe Garcia-Tsao[8]

Institutions:

[1] Department of Medicine, Division of Gastroenterology and Hepatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[2] Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland;

[3] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and CIBERehd, University of Barcelona, Spain

[4] Internal Medicine IV, Jena University Hospital, Friedrich Schiller University, Jena, Germany

[5] Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark; Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

[6] Department of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

[7] Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

[8] Yale University, New Haven, USA; VA-CT Healthcare System, West Haven, CT, USA

Author Contributions

David E. Kaplan: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration; Cristina Ripoll: Writing - Original Draft, Writing: Review & Editing, Visualization; Maja Thiele: Writing - Original Draft, Writing - Review & Editing, Visualization; Brett E. Fortune - Writing - Original Draft, Writing - Review & Editing, Visualization; Douglas A. Simonetto: Writing - Original Draft, Writing - Review & Editing, Visualization, Guadalupe Garcia-Tsao: Writing - Original Draft, Writing - Review & Editing, Visualization; Jaime Bosch: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration

Address all correspondence to:

David E. Kaplan, MD MSc

Perelman School of Medicine, University of Pennsylvania

Philadelphia, Pennsylvania, USA

dakaplan@pennmedicine.upenn.edu

Corresponding Author:

David E. Kaplan, MD MSc

3400 Civic Center Drive, PCAM 708 South,

Philadelphia PA 19104;

dakaplan@pennmedicine.upenn.edu

Phone: 215-360-0522

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Email Addresses:

David Kaplan <dakaplan@pennmedicine.upenn.edu>;

Jaume Bosch <jaume.bosch@idibaps.org

Guadalupe Garcia-Tsao <guadalupe.garcia-tsao@yale.edu

Ripoll, Cristina <Cristina.Ripoll@med.uni-jena.de

Maja Thiele <maja.thiele@rsyd.dk

Douglas Simonetto <simonetto.douglas@mayo.edu

Brett Fortune <bfortune@montefiore.org

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Abbreviations

AASLD American Association for the Study of Liver Disease
ACLD advanced chronic liver disease
AVH acute variceal hemorrhage
BRTO balloon-occluded retrograde transvenous obliteration
cACLD compensated advanced chronic liver disease
CSPH clinically significant portal hypertension
CTP Child-Turcotte-Pugh

ECI endoscopic cyanoacrylate injection

EVL endoscopic variceal ligation

FHVP free hepatic vein pressure

GV gastric varices

HE hepatic encephalopathy

LSM liver stiffness measurement

MELD Model for End-Stage Liver Disease

MRE magnetic resonance elastography

NILDA Noninvasive Liver Disease Assessment

NSBB nonselective beta-blocker

PH portal hypertension

PHG portal hypertensive gastropathy

pSWE point shear wave elastography

RCT randomized controlled trial

SSM spleen stiffness measurements

TE transient elastography

TEE transesophageal echocardiography

WHVP wedged hepatic vein pressure

1 PURPOSE AND SCOPE OF THE GUIDANCE

This Practice Guidance from the American Association for the Study of Liver Disease (AASLD) intends to coalesce best practice recommendations for the identification of portal hypertension (PH), for prevention of initial hepatic decompensation, for the management of acute variceal hemorrhage (AVH), and for reduction of the risk of recurrent variceal hemorrhage in chronic liver disease. The document updates and expands on the most recent preceding Practice Guidance from the AASLD related to the management of PH and gastroesophageal varices that was published in 2017,[1] itself an update on the initial multisociety guidelines on this topic from 2007.[2] Since this latest AASLD Practice Guidance was published, the 7th Baveno consensus conference was convened in October 2021,[3] at which international experts reviewed data related to several key randomized controlled trials (RCTs) and individual patient-data meta-analyses. Drawing from independent review of relevant studies as well as updated expert consensus, the most significant changes in the current Guidance (**Box 1**) therefore relate to (1) recognition of the concept of compensated advanced chronic liver disease (cACLD), a shift away from the requirement of a histological or radiological diagnosis of cirrhosis for initial patient risk stratification; (2) codification of methodology to use noninvasive assessments to identify clinically significant PH (CSPH); and (3) endorsement of a change in paradigm with the recommendation of early utilization of nonselective beta-blocker (NSBB) therapy when CSPH is identified in order to decrease the risk of cirrhosis decompensation.[4] The updated guidance further explores potential future pharmacotherapy options for PH, clarifies the role of preemptive TIPS in AVH, discusses more recent data related to the management of cardiofundal varices, and addresses new topics such as portal hypertensive gastropathy (PHG) as well as endoscopy prior to transesophageal echocardiography (TEE) and antineoplastic therapy. The present guidance does not focus on ascites as a complication of PH because this was recently covered in the AASLD Practice Guidance on ascites and related complications[5] and vascular causes of PH.[6] The present guidance specifically addresses PH in adults with future guidance on the management of cirrhosis in children from the AASLD anticipated.

This AASLD Guidance provides a data-supported approach to the prevention and management of PH and varices. It differs from the AASLD Guidelines, which are supported by systematic

reviews of the literature, formal rating of the quality of the evidence, and strength of the recommendations. In contrast, this Guidance was developed by consensus of an expert panel and provides guidance statements based on comprehensive review and analysis of the literature on the topic, with oversight provided by the AASLD Practice Guidelines Committee.

2 CONTEXT OF PH IN CIRRHOSIS

2.1 Definition of PH

Portal vein pressure is proportional to splanchnic blood inflow and to the resistance opposing this flow. Portal vein pressure is expressed as the portocaval pressure gradient, the pressure difference between the portal vein (venous inflow into the liver) and the inferior vena cava (that collects the venous outflow from the liver). Measurement of the gradient rather than absolute pressure eliminates influence of changes in intra-abdominal pressure.[7] In healthy participants, this pressure gradient ranges between 1 and 5 mm Hg; thus, PH in cirrhosis is defined as a gradient greater than 5 mm Hg.

In all causes of PH, an increase in resistance to portal flow is the initial pathogenic mechanism, followed by an increase in portal venous inflow.[8] The site of increased resistance forms the basis of the classification of PH into three main categories: (1) prehepatic, when the site of increased resistance occurs in the portal vein prior to entry into the liver; (2) intrahepatic, when it occurs within the liver; or (3) posthepatic when it occurs after blood exits the liver through the hepatic veins (**Table 1**). Intrahepatic PH is further subclassified into presinusoidal, with conditions that affect the portal triad; sinusoidal, when the hepatic sinusoids are affected (e.g., cirrhosis); and postsinusoidal, with conditions that affect the efferent (central) vein. By far, the most common cause of PH is cirrhosis followed by portal vein thrombosis.

2.2 Stages of cirrhosis

Histologically, the degree of fibrosis in chronic liver disease can be evaluated semiquantitatively in liver biopsy, with stages 0–2 defining early fibrosis stages, F3 bridging (advanced) fibrosis, and F4 the cirrhotic stage (if using METAVIR or Kleiner staging system), which is pathologically defined as the presence of nodules of regenerating hepatocytes separated by fibrous septa.

Clinically, cirrhosis presents in two main clinical stages: compensated and decompensated (**Figure 1**).[9] Per recent consensus definition, decompensation is defined by the development of clinically overt complications of PH,[3] specifically overt ascites, variceal hemorrhage or overt hepatic encephalopathy (HE).[3] Although the median survival in the patient who is compensated exceeds 12 years, once a patient develops a decompensating event, median survival decreases to less than 1.5 years.[10]

Decompensation most commonly occurs when portal pressure gradients are at or exceed 10 mm Hg[11–14] (measured by the hepatic venous pressure gradient described as follows). This pressure gradient defines "clinically significant portal hypertension" or CSPH.[15] Additional clinical features that are surrogate markers of CSPH include the presence of gastroesophageal varices on endoscopy and/or portosystemic collaterals on cross-sectional abdominal imaging. Because of the strong association with clinical outcomes, patients with compensated cirrhosis should be subclassified into those without and with CSPH during clinical encounters preferentially using noninvasive tests discussed in Section 4.2.

Among patients with decompensated cirrhosis, those who develop successive complications (i.e., recurrent variceal hemorrhage, refractory ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, jaundice) exhibit much higher mortality rates; this stage has now been designated as "further decompensation."[16]

Because performing a liver biopsy to establish a diagnosis of cirrhosis and/or performing HVPG measurement to establish the presence of CSPH (which is defined by an HVPG equal or greater than 10 mm Hg) are invasive tests that are not universally available, the usefulness of noninvasive tests to identify cirrhosis and/or CSPH has been explored. A new entity designated "advanced chronic liver disease" (ACLD) denotes the patient who, without a biopsy confirming it, is likely to be close to cirrhosis based on liver stiffness measurements (LSM) and platelet count, and can be applied widely as a surrogate for advanced fibrosis/cirrhosis. The term for patients with ACLD without prior decompensation is cACLD. LSM by transient elastography

(TE) <10 kPa rules out cACLD and ≥15 kPA rules in cACLD.[17–20]1 LSM by TE can be further used to rule in CSPH at values >25 kPa (in patients who are not obese).[21–23] In those with intermediate LSM values, platelet counts can be used to determine whether the patient is likely to have CSPH, following the "Rule of Five" (see Section 4.2 and Figure 3). LSM by TE should not be used for clinical decision-making without confirmation of high study quality and performance by adequately trained personnel. It is expected that other elastography technologies will have validated cutoffs to rule in and rule out cACLD and CSPH but, at the time of writing, there are insufficient data to make specific recommendations.

2.3 Resolution of PH

Reductions in portal pressure induced by pharmacological therapy or mechanically by placement of a TIPS in patients with compensated or decompensated cirrhosis decrease the risk of development of first or further decompensation and may improve survival.[8,14] Elimination of mechanical obstruction (e.g., inferior vena cava webs, portal vein thrombosis) and/or control of underlying liver disease through antivirals, immunosuppression, and alcohol cessation may also reduce portal pressure and lead to clinical recompensation and even to the resolution of cirrhosis in long-term follow-up biopsies.[16,24] In the setting of elimination or control of the underlying etiology, recompensation has been clinically defined as the resolution of ascites and/or HE no longer requiring specific therapy in the absence of recurrent variceal hemorrhage for over 12 months together with stable improvement of liver function tests (albumin, international normalized ratio, bilirubin).[3]

[1]The AASLD NILDA of Portal Hypertension does not advocate a specific cutpoint for LSM sufficient to rule in CSPH.

3 PATHOPHYSIOLOGICAL BASES OF PHARMACOLOGICAL THERAPY

3.1 Overview

In cirrhosis, the accumulation of fibrous tissue and nodule formation, with consequent vascular distortion, lead to an increase in intrahepatic vascular resistance and, subsequently, elevated portal pressure (**Figure 2**). These structural changes are followed by splanchnic vasodilation that augments portal blood flow, thereby further raising portal pressure. In addition to "fixed" parenchymal architectural distortion, a dynamic component caused by increased intrahepatic vascular tone, mostly caused by reduced nitric oxide bioavailability, accounts for about 30% of the total increase in intrahepatic resistance.[25] The pathogenesis of PH and its complications is detailed in **Figure 2**. As detailed in **Tables 2** and **3**, these mechanisms represent the main targets for pharmacologic and nonpharmacologic therapies for PH.

3.2 Which is the optimal NSBB for PH?

The beneficial effects of NSBBs in PH are derived from their ability to decrease portal pressure through a reduction in portal and collateral blood flow (**Table 3**). This is achieved by both decreased cardiac output (b-1 blockade) and splanchnic arterial vasoconstriction (b-2 blockade). Carvedilol, an NSBB that additionally exerts intrinsic anti-alpha-1-adrenergic activity and facilitates the release of nitric oxide, induces intrahepatic vasodilation further reducing portal pressure. Carvedilol allows for a significantly more pronounced decrease in HVPG than traditional NSBBs (such as propranolol and nadolol[26]).

Carvedilol achieves a marked reduction in HVPG at low doses and does not require titration based on resting heart rate. Because of liver metabolism, carvedilol is used in cirrhosis at lower doses than used for heart failure. It is recommended that therapy is started at a dose of 6.25 mg per day and, if tolerated, increased to 12.5 mg per day after 2–3 days (as a single dose or divided 6.25 mg bid), with down-titration to 6.25 mg daily (single dose or divided) if nontolerated or if systolic blood pressure falls below 90 mm Hg in compensated cirrhosis. Lower starting doses may be more appropriate in patients with Child-Turcotte-Pugh (CTP) class B and C cirrhosis.[27] About one third of patients with compensated cirrhosis have arterial hypertension. In such cases, carvedilol doses may be further up-titrated (up to 25 mg/day) for blood pressure control. Based

on its greater reduction of portal pressure in head-to-head comparisons with traditional NSBBs,[28,29] a trend for better tolerance, simpler administration, possibility of preventing ascites, and a potential survival advantage,[30,31] carvedilol is the preferred NSBB for management of PH.

3.3 Experimental pharmacological targets for prevention of progression

Novel therapeutic agents being explored to prevent or treat PH, including but not limited to statins, cGT activators/stimulators, anticoagulants, and anti-inflammatory agents (**Table 4**), broadly target endothelial dysfunction, microthromboses, and/or inflammation. HMG-coA reductase inhibitors (statins) are of particular interest following phase II studies that have shown significant effects on HVPG reduction and a single double-anonymized RCT that demonstrated improved survival with the addition of simvastatin to standard secondary prophylaxis after acute variceal bleeding.[32–34] However, there are discrepant results on whether statins have additive effect with NSBB on HVPG reduction.[32,35] Retrospective data suggest a decreased rate of progression to cirrhosis, decompensation, and death in patients receiving statins and greater reduction in HCC risk with lipophilic statins (simvastatin and atorvastatin)[36] possibly related to differential pharmacodynamics. Few prospective data exist to guide statin selection in PH except for simvastatin, which should not be used at doses greater than 20 mg/day in decompensated cirrhosis.[37] Atorvastatin metabolism is altered in cirrhosis and there is less experience with its use; as such, it may be prudent to use low doses (10–20 mg) pending additional data.[38] Presently, at least four prospective RCTs are testing physiological or clinical endpoints with statins in CTP A or B cirrhosis.[37,39,40]

Guidance statements:

1. Carvedilol is recommended as the preferred NSBB for the treatment of PH in patients with cirrhosis.
2. The recommended maintenance dosage of carvedilol is 6.25–12.5 mg/day, after initiating treatment for 2 days with only 6.25 mg at bedtime. Maintenance dosage can be given as a single dose. In patients with concomitant arterial hypertension or cardiac disease, the dose of carvedilol may be further increased to address nonhepatic indications.

4 DIAGNOSIS AND MONITORING

4.1 Hepatic vein wedge pressure measurements

Although direct portal pressure measurements can be performed by means of endoscopic ultrasound or percutaneous access, portal pressure is more commonly determined indirectly by measuring the liver sinusoidal pressure by means of a transjugular catheter placed into a hepatic vein. "Wedging" of the catheter to occlude the hepatic vein lumen is achieved either by advancing the catheter into a hepatic vein radicle or more commonly by inflating a balloon at the tip of the catheter in a large hepatic vein, the latter being considered the standard approach.[41,42] After occlusion, the pressure measured in the static column of blood equals the pressure at the sinusoids. Because in cirrhosis intersinusoidal communications are closed because of the formation of nodules and fibrous septa, the wedged hepatic vein pressure (WHVP) is equivalent to the portal vein pressure. The difference between WHVP and unwedged "free hepatic vein pressure" (FHVP; measured with the tip of the catheter introduced about 2–3 cm into the hepatic vein) is the HVPG, approximating the portacaval pressure gradient.

Accuracy of HVPG measurements can be increased (1) by using balloon catheters to occlude the hepatic vein (averaging the pressure in a larger territory); (2) by obtaining triplicate measurements; and (3) by following several simple measurement conventions (**Box 2**).[41,42] HVPG provides valuable prognostic information in compensated and decompensated cirrhosis at baseline,[41–44] in response to vasoactive drug therapy (such as beta-blockers),[44–47] after elimination of the cause of cirrhosis,[13,42,48,49] prior to resection operation for HCC,[50] and prior to any major operation in patients with cirrhosis.[51]

HVPG measurement does not accurately estimate portal pressure in presinusoidal PH, characteristic of noncirrhotic primary biliary cholangitis, granulomatous diseases, and portosinusoidal vascular disorder (previously referred to as idiopathic PH or noncirrhotic intrahepatic PH, with nodular regenerative hyperplasia or periportal sclerosis as main histological hallmarks).[42] In such cases, endoscopic screening for complications of PH is recommended. Although HVPG measurement may also be inaccurate in some patients with

NASH[52]; HVPG values, changes in HVPG, and CSPH do retain prognostic significance among patients with NASH.[53,54]

Although measurement of HVPG has become the gold standard to assess the presence and quantify the degree of PH,[41] it is moderately invasive and carries small risks of injury related to access of the jugular vein, induction of arrhythmias, and exposure to radiation.[55] Interpretation of HVPG also requires specific expertise. Together, these limitations restrict its routine use to specialized centers and as such have stimulated efforts to validate noninvasive surrogates usable in regular clinical practice.

4.2 Noninvasive detection of CSPH

Conventional cross-sectional imaging such as ultrasound, CT, and MRI have a limited but defined role for identifying CSPH. Specific imaging surrogate markers of CSPH include visualization of collaterals (periesophageal varices, recanalization of the umbilical vein, presence of splenorenal shunt) and presence of ascites. Doppler-based sonographic assessments of hepatic artery waveforms, pulsatility, or other surrogate markers of CSPH have moderate sensitivity and specificity[56] and are not widely applied.

The best validated noninvasive staging system for *compensated* cirrhosis is based on LSM by TE (FibroScan, Echosens, France) and platelet count (**Figure 1B**).[3,57] The "Rule of Five" has been proposed as a simple tool to quantify increasing relative risk of decompensation and liver-related mortality and to define cACLD, CSPH, and the threshold for screening upper endoscopy (**Figure 3**). Caution should be used in applying the "Rule of Five" in patients with obesity and NAFLD/NASH, alanine aminotransferase increased >3× upper limit of normal, and primary sclerosing cholangitis with dominant stricture(s) caused by poorer calibration.[22,58] For patients with chronic viral hepatitis, alcohol-associated liver disease, and lean NAFLD (body mass index < 30 kg/m^2), an LSM exceeding 25 kPa has a positive predictive value of >90% for CSPH; however, the positive predictive value for this cutoff in patients with obesity and NASH is only 63%.[22]

There are insufficient data to support the utilization of any serological markers such as platelet count alone or enhanced liver fibrosis to exclude CSPH and eliminate the need for endoscopy assessment to detect varices needing treatment.

Currently, the most robust estimation of CSPH is provided by the combination LSM (by TE) and platelet count (**Figure 3**).[21,22,58] CSPH can be presumed in the presence of (1) LSM > 25 kPa, (2) LSM between 20 and 25 kPa and platelets < 150 K/mm^3, or (3) LSM between 15 and 20 kPA and a platelet count < 110 K/mm^3. CSPH can be excluded in patients with LSM < 15 kPa plus platelets > 150 k/mm^3. These cutoff values are highly specific, but there remains room for refinement because many patients remain unclassified ("gray zone"). Liver stiffness-spleen size-to-platelet ratio has also proven to be an accurate surrogate marker of CSPH with values > 2.65 corresponding to a risk of CSPH above 80%.[58,59]

When HVPG values exceed 10 mm Hg, spleen stiffness measurements (SSM) by TE show a stronger correlation with HVPG than LSM.[60] SSM ≤ 46 kPa may be particularly suited for ruling out varices needing treatment and eliminating need for endoscopy for patients who would otherwise be selected for screening endoscopy using Baveno VI criteria (LSM ≥ 20 kPa, platelets <150 K/mm^3).[57,61,62] Spleen length has been suggested as a proxy for spleen stiffness because the two exhibit a strong linear correlation.[63] However, the clinical utility of SSM and spleen length remains to be validated because of (1) inclusion of only patients with chronic viral hepatitis, limiting generalizability to ALD and NAFLD; (2) high technical failure rates (15%–27%) for SSM; and (3) need for validation of a novel 100 Hz spleen-dedicated probe.

For LSM, non-TE elastography methods, such as magnetic resonance elastography (MRE), point shear wave elastography (pSWE), and two-dimensional shear wave elastography, have been less well validated and may be subject to cross-manufacturer variability. MRE and pSWE may be used to rule out cACLD across etiologies using platform-specific normal values (**Figure 3**). Several studies, primarily in NAFLD, have evaluated MRE for fibrosis assessment on 1.5T MRI scanners with shear wave frequencies around 60 Hz.[64–67] Although there may be some minor differences between equipment at these settings, MRE <3.5 kPa generally rules out cACLD, and ≥5.0 kPa rules in cACLD.[66,67] Fourteen studies have evaluated MRE for prediction of complications related to PH, but only two compared MRE with the gold-standard HVPG.[67–70] In the largest, most recent study, using Siemens 1.5T equipment, a cutoff of 7.7 kPa diagnosed CSPH with a moderate sensitivity of 78% and low specificity of 64%. For pSWE, an LSM cutoff of greater than 2.17 m/s may identify CSPH.[56] Cutoffs for LSM measured by non-TE elastography methods (MRE, pSWE, two-dimensional shear wave elastography) or laboratory-based tests to define CSPH are not currently validated, as reviewed in the AASLD Noninvasive Liver Disease Assessment (NILDA) Guideline.[71]

Because of its well-established value in the clinical evaluation of patients with ACLD, liver elastography measurements should be available in all centers caring for patients with ACLD. NILDA are best calibrated for chronic viral hepatitis and ALD etiologies but tend to overestimate CSPH risk in patients with obesity and NAFLD.[22] Promising, but small and nonexternally validated, studies have reported good correlation of contrast-enhanced ultrasound-derived,[72] MRI,[73] and serum biomarkers[74–77] with HVPG. However, as reviewed in the AASLD NILDA Guideline, correlations between blood-based NILDA and CSPH remains inferior to those with imaging-based NILDA.[71] In the absence of LSM or sleep stiffness, platelet count has only modest predictive value for identifying CSPH[78] and no data-supported recommendation can be made regarding the use of platelet counts in isolation to guide endoscopic surveillance or NSBB initiation.

4.3 Monitoring the development of CSPH, varices, and high-risk varices in the natural history of cirrhosis

Longitudinal studies investigating LSM by TE as a monitoring tool[79–84] suggest three clinical scenarios in which serial monitoring of patients with chronic liver disease using NILDA are of relevance: (1) monitoring progression in patients with initial LSM 5–10 kPa in whom repeating LSM every 2–3 years may be reasonable, individualizing intervals based on individual risk of progression[20]; (2) confirming an initial LSM suggestive of cACLD to reduce false positive findings,[85–87] particularly in populations with low prevalence[88]; (3) monitoring progression in patients with initial LSM diagnostic of cACLD without CSPH, in whom repeating LSM by TE and platelet count annually would be indicated to identify patients for whom NSBB should be initiated or screening endoscopy should be performed.[3]

In published studies of cohorts of patients with viral hepatitis or NASH, a ≥20% increase or decrease in LSM by TE appears to correlate with clinically relevant deteriorations or improvement. In two studies in which a 20% increase or decrease was used as a predefined endpoint, an increase of >20% was associated with increases in hepatic decompensation, whereas a decrease of >20% was associated with decreased mortality.[82,83] A third study found an average 22% increase in LSM in patients with HCV who decompensated during follow-up, whereas patients free of decompensation decreased LSM by 21%.[84] Consequently, monitoring LSM in cACLD should only be performed if a 20% change (increase or decrease) would alter patient management.

There is no role of measuring baseline or serial LSM in decompensated cACLD (by definition with CSPH) unless clinical recompensation has occurred and discontinuation of NSBB or other decompensation-related therapy is being considered.

4.4 Monitoring changes in HVPG related to therapy

There is no role of LSM or SSM for monitoring HVPG response to NSBB in the short- or long-term because there is no correlation with HVPG in this setting.[89,90] SSM has been proposed as a better marker of changes in PH, but MRE-measured SSM did not correlate with acute NSBB response in one small study.[68]

Guidance statements:

3. HVPG measurement is the gold-standard method to assess portal pressure in patients with cirrhosis.
4. CSPH is defined as HVPG ≥ 10 mm Hg.
5. HVPG may underestimate portal pressure in some patients with obesity and NASH-related cirrhosis.
6. The presence of clinical decompensation, of gastroesophageal varices on endoscopy, or portosystemic collaterals or hepatofugal flow on imaging is sufficient to diagnose CSPH.
7. CSPH can be noninvasively identified by LSM by vibration-controlled TE (or non-TE approaches when validated cutoffs exist) and platelet count. CSPH is diagnosed at LSM ≥25 kPa irrespective of platelet count, LSM 20–24.9 kPa with platelet count < 150 K/mm^3, or LSM 15–19.9 kPa with platelet count <110 K/mm^3.
8. Annual LSM by TE (or non-TE approaches when validated cutoffs exist) and serum platelet counts may provide prognostic information in patients with cACLD without baseline CSPH in whom the underlying etiologies of cirrhosis remain active/uncontrolled.

5 STAGE-SPECIFIC MANAGEMENT OF PH

5.1 Compensated cirrhosis without CSPH but with mild PH (HVPG 6–9 mm Hg)

As mentioned in Section 2.2, patients with cACLD can be subcategorized according to the presence or absence of CSPH. The presence of CSPH is associated with an increased risk of clinical decompensation[91] (see Section 5.2).

All patients with compensated cirrhosis should undergo regular imaging (every 6 months per AASLD guidance[92]) to screen for HCC and portal vein thrombosis. In patients without CSPH, special attention should be paid to imaging evidence indicating development of CSPH, such as detection of large collaterals (i.e., recanalization of the umbilical vein or splenorenal shunt) or presence of hepatofugal blood flow in the main portal vein.[93]

Among patients without CSPH for whom NSBBs to prevent decompensation are contraindicated or in whom intolerance to beta-blockers is known, serial assessment for the need for EGD to identify high-risk varices remains important. Use of LSM measurement in combination with platelet count (LSM < 20 kPA and platelet count > 150 K/mm^3, also known as Baveno VI criteria) can identify patients in whom the likelihood of high-risk varices is very low and therefore screening EGD can be avoided.[94] A reevaluation of these patients with platelet count and LSM is recommended on a yearly basis.[95,96] If LSM is not available, endoscopic surveillance to identify CSPH should be performed unless there are surrogates of PH identified by imaging, such as portosystemic collaterals. If identified, CSPH can be presumed and NSBB be initiated. There are insufficient data to recommend restricting endoscopy to candidates with platelet counts < 150 K/mm^3 in the absence of TE (see Section 5.3).

Treatment with beta-blockers in compensated cirrhosis without CSPH (previously termed "pre-primary prophylaxis") is not indicated because beta-blockers do not reduce the incidence of new varices, variceal bleeding, or clinical decompensation at this stage.[91,97]

Suppression or cure of the etiological cause of the liver disease, lifestyle optimization (adequate nutrition, normal body weight, avoidance of alcohol and other toxic substances) and control of comorbidities attenuate and/or reverse the progression of the liver disease.[98–100] In NAFLD/NASH, obeticholic acid (contraindicated with PH), lanifibranor, and semaglutide have shown early promise in reducing fibrosis in patients who are noncirrhotic.[101–103] It is presumed that improvement of fibrosis would prevent CSPH and have a positive impact on the natural history of cACLD.

Finally, some widely used medications for other indications may have beneficial effects in cirrhosis and should not be discontinued because of recognition of cACLD. The possible benefits of statins on cACLD have been discussed in Section 3.2. There are studies suggesting that metformin could be safe[104,105] and may reduce HVPG after a single dose,,[106] the incidence of HCC, and decompensation in compensated cirrhosis.[104,105] Similarly, use of low-dose aspirin might also reduce the incidence of HCC and liver-related mortality in patients with chronic hepatitis B and C and seems to be safe in patients with compensated cirrhosis.[107]

Guidance statements:

9. Use of NSBBs in patients with cirrhosis without CSPH is not recommended for prevention of decompensation.
10. Lifestyle modification and treatment of underlying liver disease should be prioritized to prevent progression to CSPH and decompensation.

5.2 Compensated cirrhosis with proven or likely CSPH (HVPG ≥ 10 mm Hg)

Patients with compensated cirrhosis with CSPH as defined by an HVPG ≥ 10 mm Hg are at increased risk of decompensation. Given low access and/or acceptance of HVPG measurements, other methods to detect CSPH can be used in the clinic. The presence of portosystemic collaterals, including varices of any size, on endoscopy or imaging can be used as a surrogate marker of CSPH.[93,108] Additionally, TE can identify patients with CSPH (see Section 4.2)

Data from two prospective trials provide support for initiation of NSBB to prevent decompensation in cACLD with CSPH. The PREDESCI study included 201 patients with compensated cirrhosis with CSPH without high-risk varices who were randomly assigned to a beta-blocker (propranolol or carvedilol, according to the acute hemodynamic response to propranolol) or placebo.[4] NSBB were up-titrated to clinical tolerance as well as to maintain pulse ≥ 55 bpm and systolic blood pressure ≥ 90 mm Hg with planned upper limits of 160 mg and 25 mg for propranolol and carvedilol, respectively. However, the mean dosages of propranolol and carvedilol actually achieved post-titration were 95 mg/day and 19 mg/day, respectively. After 2 years of clinical follow-up, patients treated with NSBB manifested significantly lower risk of decompensation (HR, 0.51; 95% CI, 0.26–0.97), predominantly a lower risk of developing ascites, recently confirmed in a Bayesian reanalysis.[109] Some caution should be made with applying these findings to all patients with compensated cirrhosis and CSPH because of the unique selection criteria of patients for this study; all patients had confirmed CSPH by HVPG and were not selected for inclusion by NILDA. Additionally, the majority of patients had untreated hepatitis C prior to availability of all-oral direct antiviral therapy, and the effect of ongoing alcohol use was not assessed. In subgroup analysis, patients

with nonalcoholic liver disease and small varices appeared to have greater benefit from carvedilol.

In the absence of imaging surrogates of CSPH, in which TE is not available, patients with cACLD should undergo surveillance endoscopy. Current guidance related to surveillance intervals relies predominantly on expert consensus based on studies of the natural history of variceal progression.[97,110–112] The prevalence of varices among patients who were compensated at baseline endoscopy was approximately 25%; among those without varices, new varices were detected at a rate of approximately 4.4–5% per year; conversion from small to medium or large varices occurred within 1–2 years in 10–20% of individuals; annual incident bleeding occurred within 1 year in approximately 15% of cases with large varices; and that the natural history is significantly impacted by ongoing liver injury, in particular continued alcohol use.[113] Based on this natural history, consensus guidelines have evolved recommending that patients with cACLD without varices who have ongoing liver injury should have endoscopy repeated every 2 years, and those without varices in whom liver injury is quiescent, e.g., after suppressing hepatitis B virus replication or obtaining a sustained virological response (SVR) in patients with hepatitis V virus infection, and alcohol abstinence, should undergo variceal surveillance every 3 years. Emerging data suggest that particularly post-SVR, liver decompensation in patients who were previously compensated may be so infrequent that surveillance may be discontinued after the first surveillance endoscopy shows no varices.[114]

Guidance statements:

11. In patients with compensated cirrhosis and CSPH, the goal of therapy is to prevent the development of clinical decompensation.
12. NSBBs (preferably carvedilol 12.5 mg/day) should be considered for patients with cACLD with CSPH to prevent decompensation.
13. NSBBs should not be administered to patients with cACLD and evidence of CSPH with asthma, advanced heart block, and bradyarrhythmias, and caution should be used in patients with relative contraindications (Box 2).
14. Screening endoscopy is not necessary in patients who are compensated or decompensated and on NSBB therapy; the need for screening endoscopy can be obviated in some patients

on a selective beta-blocker by switching therapy to an NSBB after discussion with the prescribing clinician.

15. Patients with cACLD and evidence of CSPH (by endoscopy, TE, HVPG, or imaging) who are candidates for NSBB should be considered for treatment with NSBB (in the absence of contraindications) to prevent hepatic decompensation, which would also obviate the need for further screening endoscopy.
16. Where TE is not available to diagnose CSPH, when empiric NSBB are contraindicated or not considered because of prior intolerance, endoscopic surveillance of all patients with cirrhosis is recommended. Patients with cACLD without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence). Patients with cACLD without varices who develop decompensation should have a repeat endoscopy when this occurs. The presence of varices of any size should prompt initiation of NSBB (in absence of contraindication).

5.3 Compensated cirrhosis with a contraindication to or intolerance of beta-blockers

Patients with compensated cirrhosis who have contraindication for beta-blockers (see **Box** Error! Reference source not found.**3**) or who do not tolerate beta-blockers have at present no further therapeutic options to avoid clinical decompensation other than control of the underlying disease. Although a possible benefit of statins to prevent decompensation in this setting is pathophysiologically plausible[32] and retrospective studies suggest that statins reduce the incidence of decompensation,[115,116] to date, there are insufficient data to recommend its routine use. Patients with a standard indication for statin therapy should continue treatment, and statins should not be discouraged when indicated.

In patient with cACLD with CSPH for whom beta-blockers cannot be safely administered, endoscopic surveillance should be initiated with an intent to prevent first variceal hemorrhage (primary prophylaxis) through prophylactic endoscopic band ligation of high-risk varices. Performance of an endoscopy every 2 years is recommended; however, if cause of the liver disease is under control (alcohol abstinence, weight control, viral suppression or elimination,

etc.), endoscopic surveillance may be done every 3 years.[94] In some cases, cessation of surveillance may be considered after negative serial endoscopic assessments in the setting of complete disease resolution (e.g., sustained sobriety, SVR after HCV direct-acting antiviral therapy with complete normalization of aspartate aminotransferase and alanine aminotransferase), LSM < 12 kPa, and platelet > 150 K/mm^3.[117]

If endoscopic variceal ligation (EVL) is selected for primary prophylaxis of high-risk varices, EVL should be repeated until all varices are eradicated. Intervals between endoscopies evaluated in clinical trials for primary and secondary prophylaxis have ranged from 1 to 8 weeks.[118–123] In a prospective randomized trial for secondary prophylaxis, no difference in overall obliteration rates after 3 endoscopy sessions was demonstrated in patients undergoing repeat endoscopy every 2 weeks (at week 2 and week 4) compared with those selected to undergo endoscopy every 8 weeks (at week 8 and week 16), with persistent banding ulcers only observed in the every 2 week arm, and higher rates for reintervention during long-term follow-up required in the every 2 week arm.[124] In a more recent study, repeat endoscopy after AVH every 1 week showed no superiority to repeat endoscopy every 2 weeks until eradication with regard to recurrent bleeding, safety, or mortality.[125] Based on limited data, a recommendation was made for an interval of 2–4 weeks, favoring 4 weeks to allow banding ulcers to heal. After eradication, periodic endoscopy should be repeated every 6–12 months.

Studies from the 1960s and 1970s showed that the use of surgical shunts to prevent first variceal bleeding increased the incidence of HE and increased mortality.[126] It has been extrapolated from these data that prophylactic TIPS to prevent first variceal hemorrhage in the setting of compensated cirrhosis with high-risk varices should not be recommended.

Guidance statements:

17. Patients with compensated cirrhosis and CSPH without varices who have contraindications or intolerance to beta-blockers should be screened for varices needing treatment with surveillance endoscopy every 2 years when the underlying disease remains uncontrolled and every 3 years when controlled.

18. Patients with compensated cirrhosis and CSPH with varices that have not bled who have contraindications or intolerance to beta-blockers should be screened for varices needing treatment with surveillance endoscopy every 1 year when the underlying disease remains uncontrolled and every 2 years when controlled.
19. Primary prophylaxis with EVL should be performed in patients with cACLD and CSPH and high-risk varices that cannot receive NSBBs.
20. Band ligation should be repeated every 2–4 weeks until obliteration and then endoscopy repeated at 6 months and then every 12 months to assess for reappearance of varices requiring additional treatment.
21. TIPS should not be used for the prevention of decompensation of cirrhosis or as primary prophylaxis for variceal hemorrhage.

5.4 Primary prophylaxis to prevent variceal hemorrhage in dACLD

Patients who have decompensated cirrhosis by definition have CSPH. Increasing CTP class, variceal size, and presence of variceal red wale marks are associated with an increase in the risk of a first variceal hemorrhage.[127] Patients with high-risk varices (moderate/large varices or any size varices with red wale marks or in a patient with CTP C) should undergo primary prophylaxis to prevent variceal bleeding. If the high-risk varices are small, the only method that is technically feasible is the administration of NSBB. If the high-risk varices are large, both NSBB as well as EVL are possible approaches; however, a recent systematic review with network meta-analysis showed that EVL is associated with a higher risk of complications and higher mortality than NSBB.[128] The administration of carvedilol in patients with high-risk varices and ascites has been associated to an improved survival in a prospective study (HR, 0.41; 95% CI, 0.19–0.96)[129] and a retrospective study (HR, 0.61; 95% CI, 0.46–0.81).[130] A retrospective long-term follow-up of patients included in a previous RCT comparing carvedilol to EVL for primary prophylaxis, in which half of the patients had ascites and approximately two thirds of the patients were CTP class B and C at baseline, found a survival benefit related to randomization to carvedilol compared with EVL (median survival of 7.8 versus 4.2 years).[131] This effect could be mediated by a decrease in the incidence of further decompensation among patients who receive NSBB.[14,132–134]

The safety of NSBB among patients who have ascites and refractory ascites has been an issue of extensive discussion in the past decade since an initial publication suggesting an increased mortality among patients with refractory ascites and beta-blockers.[135] However, in this study most patients were given unusually high doses of propranolol (160 mg of long-acting propranolol per day). In the interim, several studies have shown that NSBB in patients with ascites and even refractory ascites are safe and potentially beneficial.[136–140] However, low systolic blood pressure (<90 mm Hg) may attenuate the survival advantage associated with NSBB use[141,142] possibly by reducing renal perfusion pressure increasing the risk of hepatorenal syndrome–acute kidney injury.[143] In patients who have low arterial blood pressure with low doses of carvedilol, one may consider a switch to a traditional NSBB such as propranolol or nadolol because these agents usually have lesser effects on arterial pressure.[142,144]

Guidance statements:

22. Patients with decompensated cirrhosis not taking NSBBs who have never bled from varices should undergo annual endoscopic screening.
23. If high-risk varices are detected, NSBBs or endoscopic band ligation are recommended; preference is given to NSBBs (including carvedilol) because of benefits beyond prevention of variceal hemorrhage. (If endoscopic band ligation is chosen, refer to recommendation 19).
24. NSBBs should be dose reduced or discontinued in patients who develop persistently low systolic arterial pressure <90 mm Hg or severe adverse effects. NSBB discontinuation should prompt endoscopic evaluation for presence of high-risk varices requiring band ligation.

5.5 AVH, initial bleed

AVH remains an emergent complication of cirrhosis and requires timely and effective management to prevent short-term mortality. Even with therapeutic advancements for AVH, 6-week mortality still ranges from 10% to 15%.[1,94] Hemorrhage results from variceal wall rupture because of increased wall tension, itself related to elevated variceal transluminal pressure, increased variceal diameter, and decreased wall thickness.[145] The incidence of AVH correlates with the magnitude of PH (HVPG measurement, NILDA), severity of liver disease (e.g., CTP

class or Model for End-Stage Liver Disease [MELD] score), and varix characteristics (size, red wale signs).[44,146–149] Most deaths from AVH occur in patients with CTP C; patients with CTP A rarely die from variceal bleeding. Tailoring treatment approaches to patient characteristics therefore remains critical.

The mainstay of AVH management includes maintaining adequate systemic organ perfusion and oxygenation while achieving hemostasis but avoidance of worsening portal pressure (**Figure 4**). On presentation of gastrointestinal hemorrhage, those with known or suspected history of advanced liver disease should be managed as having a portal hypertensive-related source until endoscopic confirmation. Patients presenting with AVH should be transferred to a medical care unit that provides proper levels of nursing and medical care, such as an intensive care unit. Placement of adequate intravenous access and airway assessment are initial measures for resuscitation. For those with altered mentation or risk of aspiration, an endotracheal tube should be placed prior to upper endoscopy. Given increased mortality risk while intubated, providers should attempt extubation as soon as deemed safely possible.[150] Vasoactive therapy (**Table 5**) that is aimed to reduce portal pressure and collateral blood flow[151,152] as well as antimicrobial prophylaxis should be initiated immediately on presentation and maintained for 2–5 days.[1,151,152] Intravenous antimicrobials are recommended until stability for discharge or 5 days, whichever is shorter, in the absence of active infection. Intravenous ceftriaxone dosed at 1 g every 24 hours is often preferred because of high rates of quinolone resistance; however, systemic antimicrobial choice should be tailored to local hospital antimicrobial resistance and stewardship policies.[153–156] Because aspiration pneumonia is the most common infection to develop in patients admitted for variceal bleeding,[157] care should be taken at endoscopy and any intervention that involves the airway; routine pre-endoscopic or preintubation placement of nasogastric tubes should be discouraged. Packed red blood cell transfusion goals should be restricted for a target hemoglobin of about 7 g/dL in the absence of comorbidities (e.g., ischemic coronary disease) or instability that might merit higher targets.[158,159] Furthermore, coagulation parameters such as international normalized ratio do not predict hemostatic dysfunction, and liberal transfusion of frozen plasma and other blood products should be avoided to prevent worse survival and worsening portal pressure.[158,160,161] Once the patient is stable, abdominal imaging with either contrast-enhanced cross-sectional modality (CT or MRI) or ultrasonography with Doppler should be performed to

evaluate for portal venous thrombosis as well as presence of liver cancer. In addition, cross-sectional imaging would assist in patients needing endovascular procedures.

Timely upper endoscopic evaluation should be performed (within 12 hours of AVH presentation) to determine source of bleeding and therapy.[162,163] If varices are visualized, the endoscopist can determine location of varices, if actively bleeding, and presence of varix characteristics (large column size, red wale signs). EVL, repeated after discharge every 2–4 weeks until variceal obliteration, should be the standard endoscopy approach for esophageal varices.[164] Intravenous erythromycin 125–250 mg given 30–120 minutes before endoscopy has been shown to facilitate visualization and therapy.[165,166] Management of bleeding gastric and ectopic varices will be discussed as follows. If immediate hemostasis is not achieved, patients with ongoing bleeding should have endotracheal tube placement and proceed with balloon tamponade or esophageal stenting as a temporizing measure. Depending on local availability and expertise, use of specialized esophageal self-expandable metal stents (not FDA approved in the United States) can also be used to achieve hemostasis with similar efficacy and improved safety compared with balloon tamponade.[167–169] Esophageal stents have the advantage that they can be kept in place for up to 1 week, compared with balloon tamponade, which is limited to 24 hours. Emergent placement of TIPS using a polytetrafluoroethylene-covered stent may be considered before removing balloon tamponade or esophageal stent.[170] Many centers administer prophylactic lactulose or rifaximin to decrease the risk of HE after TIPS based on data from RCTs.[171,172]

For specific patients who are high risk and have AVH, "early" or preemptive TIPS improves both bleeding control as well as survival in most[49,173–175] but not all studies.[176] Specifically, patients with CTP class B score > 7 with active bleeding on endoscopy and CTP class C score 10–13 should undergo TIPS within 24–72 hours of initial endoscopy. Similar recommendations are made for those who have had HVPG measurements > 20 mm Hg obtained,[177] although measuring pressure in this setting is challenging and is not recommended. It is important to emphasize that studies that evaluated early TIPS excluded older and pregnant patients, patients with nonearly stage HCC, severe acute or chronic kidney disease, patients on secondary prophylaxis for prior hemorrhage, nonesophageal variceal bleeding, complete portal vein thrombosis, and heart failure. In retrospective studies, high rates of mortality despite intervention

have been observed in this setting for patients with MELD score > 19,[178,179] but early TIPS is still associated with lower mortality than standard therapy.[179] Transplant candidacy should be promptly assessed in such patients. For those who have early hemostasis but develop rebleeding within the first 5 days post-bleed, providers may proceed with repeat endoscopy and treatment based on findings; however, this is a high-risk situation for which "rescue" TIPS may be the optimal approach in the absence of contraindications.[170]

Once hemostasis, hemodynamic stability, and normal mentation have been restored, oral nutrition must be started immediately to avoid malnutrition.[180] Proton pump inhibitors should be discontinued in the absence of absolute indications because of increased risk of infection and encephalopathy.[181–183] NSBBs can be introduced once patients can tolerate oral intake. Vasoactive therapy should be subsequently discontinued concomitant with NSBB initiation and not later than day 5.

Guidance statements:

25. All patients with known or suspected cirrhosis presenting with acute gastrointestinal bleeding should be initiated on vasoactive therapy (e.g., somatostatin, octreotide or terlipressin if available; see **Table 5**) and intravenous antibacterial therapy as soon as possible.
26. If portal hypertensive bleeding is confirmed at endoscopy, vasoactive therapy should be continued for 2–5 days.
27. Intravenous antibacterial treatment should be tailored to local resistance patterns and patient allergies. The most commonly used agent is ceftriaxone 1 g/24 hours up to 5 days. Antimicrobial therapy can be discontinued once bleeding is controlled and in absence of an active infection.
28. Packed red blood cell transfusions should target a hemoglobin ~7 g/dL unless higher targets required related to comorbid conditions.
29. Fresh frozen plasma and platelet transfusions should not be administered based on international normalized ratio or platelet count targets, respectively, because there is no evidence of benefit of such transfusions in AVH, and in the case of fresh frozen plasma, there is evidence of potential harm.

30. Upper endoscopy should be performed within 12 hours of presentation with AVH.
31. If esophageal variceal bleeding is confirmed, EVL should be performed.
32. In patients with CTP class B score > 7 and active bleeding on endoscopy or CTP class C score 10–13, preemptive TIPS creation (within 72 hours and ideally within 24 hours of initial upper endoscopy) should be recommended in absence of absolute contraindications to TIPS. If TIPS is not locally available, transfer to a center with the capacity to intervene should be considered.
33. In patients presenting with AVH who do not undergo TIPS, NSBB should be initiated at discontinuation of vasoactive therapy.
34. Covered expandable esophageal stents (where available) or balloon tamponade should be considered in patients with uncontrolled AVH as a bridge to TIPS.
35. TIPS should be considered in patients with uncontrolled AVH ("salvage" TIPS) or who rebleed despite vasoactive therapy and EVL ("rescue" TIPS).
36. Enteral feeding should be started once AVH episode has been controlled. The presence of variceal bands does not contraindicate placement of a feeding tube if indicated.
37. Proton pump inhibitors should be discontinued once AVH has been confirmed as the bleeding source in the absence of other specific indications.

5.6 Prevention of recurrent hemorrhage after initial bleeding

After an episode of first AVH, patients are at high risk of rebleeding (up to 60% at 1 year without prophylaxis).[126] Secondary prophylaxis to prevent rebleeding should be instituted immediately after control of the index bleed, within 7 days from admission, because the highest risk period for rebleeding is the first 6 weeks after presentation.[184] In patients who underwent preemptive TIPS, no further measures are required. Those without preemptive TIPS should receive secondary prophylaxis with NSBBs and endoscopic band ligation.[185–187] When compared with EVL alone, the combination of EVL and NSBB reduced rebleeding in all categories of patients and improved survival in patients with CTP class B and C.[188] Propranolol, nadolol, and carvedilol may be used for secondary prophylaxis[28]; carvedilol has greater effects on HVPG reduction but a higher potential to cause systemic hypotension.[189] The use of isosorbide mononitrate to enhance the portal pressure response to NSBBs has been almost abandoned since the advent of carvedilol. A multicenter double-anonymized RCT disclosed a

reduced mortality when simvastatin was associated to propranolol and EVL in patients surviving an episode of AVH, which was related to preventing deaths after acute-on-chronic liver failure precipitated by infections or bleeding.[32] These findings, although supported by experimental data,[190] await clinical confirmation.

When AVH occurs despite primary prophylaxis, patient adherence with EVL and NSBB, and NSBB dosage, should be evaluated. True failure of primary prophylaxis with NSBB (propranolol or nadolol) is associated with a persistently high risk of rebleeding and death despite addition of EVL[191] for secondary prophylaxis. In such patients, one may consider adding isosorbide mononitrate,[192] switching the NSBB to carvedilol given its greater portal pressure-reducing effect,[189] or consider adding simvastatin to NSBB and EVL, a strategy that in a single RCT was associated with reduced mortality despite no effect on variceal rebleeding.[32,33] Simvastatin should be used with caution in patients with total bilirubin > 3 mg/dL and used only at low doses (10–20 mg/day) in patients with CTP B–C because of the risk of rhabdomyolysis.[37]

TIPS when used as first-line therapy for secondary prophylaxis is associated with lower rebleeding rates compared with EVL + NSBB but has no impact on survival and is associated with higher rates of HE.[193,194] Therefore, TIPS placement as first-line approach for secondary prophylaxis should be reserved for patients with other indications for TIPS, such as recurrent/refractory ascites, where it may improve survival.[195] The use of TIPS as first option in secondary prophylaxis in other high-risk groups has not been adequately studied so far. TIPS is recommended for patients who rebleed despite adequate secondary prophylaxis, especially those with rebleeding within the first 6 weeks.[196]

Guidance statements:

38. Patients with variceal bleeding who do not fulfill the criteria for a preemptive TIPS and/or do not undergo TIPS during admission should undergo secondary prophylaxis with NSBB and endoscopic band ligation.
39. Use of TIPS for secondary prophylaxis can be considered in patients with additional indications for TIPS (e.g., refractory ascites).

6 GASTRIC AND ECTOPIC VARICES

Gastric varices (GV) are commonly classified according to the Sarin classification.[197] This classification divides GV among those that are a continuation of esophageal varices along the lesser curvature (GOV1) or greater curvature (GOV2) and isolated GV, which can be found in the fundus (IGV1) or in other areas of the stomach (IGV2). Varices along the lesser curvature (GOV1) share a natural history and can be treated comparably with esophageal varices. Varices along the greater curvature (GOV2) and in the fundus (IGV1) are frequently referred to as cardiofundal or gastric fundal varices and have a different natural history than esophageal varices. Although acute hemorrhage from esophageal varices occurs far more commonly, bleeding cardiofundal varices are associated with higher rates of treatment failure, rebleeding, and mortality.[197–199]

The prevalence of GV ranges between 17% and 25% among patients with cirrhosis that have not bled. GV are more common among patients with prehepatic PH, particularly in those with splenic vein thrombosis causing left-sided or sinistral PH, than among those with sinusoidal PH.[1,42,197–203] Therefore, when GV are identified, contrast-enhanced cross-sectional imaging should be performed to rule out vascular thrombosis.[203] The presence of GV or ectopic varices indicate the presence of CSPH,[93] but GV typically evolve and bleed at lower portal pressure than do esophageal varices.[202] The incidence of bleeding from cardiofundal varices is reported around 16% and 45% at 3 years.[198,199] Predictors of bleeding among patients with GV appear similar to those of esophageal varices: size (>10 mm for cardiofundal varices), presence of red marks, and liver disease severity.[1,127,204–206]

Rectal, stomal, and other ectopic varices may be identified among patients with cirrhosis and CSPH.[207,208] Although rectal varices appear to have low bleeding rates, small intestinal varices (resulting from previous intestinal operation) may exhibit high rates of bleeding and associated mortality.[208] Few systematic data exist for the management of patients with these varices, and the management principles and approaches for GV should generally be applied. Surgical management is sometimes required in patients with compensated cirrhosis for stomal and small bowel varices with bleeding refractory to NSBB and transvenous therapy.

6.1 Prevention of bleeding

Patients with compensated cirrhosis with GV who have not experienced acute hemorrhage do have CSPH and should be evaluated for NSBB therapy with a goal of preventing rebleeding and decompensation.[4] The role of primary endoscopic or endovascular prophylaxis (TIPS, balloon-occluded retrograde transvenous obliteration [BRTO]) to prevent first hemorrhage in cardiofundal varices remains unclear because there are a few studies that include a very low numbers of participants[199,209,210] (Supplemental Table 1, http://links.lww.com/HEP/I69). One RCT showed that the use of cyanoacrylate injection is superior compared with NSBBs to prevent a first bleeding episode in patients with cardiofundal varices ≥ 10 mm in a population that included adults and children with compensated and decompensated cirrhosis; however, no survival benefit was demonstrated.[199] Performance of endovascular procedures is feasible to prevent initial hemorrhage in cardiofundal varices and has been reported effective in case series[209,210]; however, because of the overall paucity of data and relatively high incidence of portal hypertensive complications after BRTO,[211] no formal recommendations regarding primary prophylaxis using endoscopic or endovascular therapy can be made at present.

Ectopic varices, referring to varices located outside of the esophagus and proximal stomach, such as IGV2, duodenal, jejunal, rectal or stomal sites, are uncommon but can cause substantial bleeding. Similar to GV, ectopic varices more commonly occur with prehepatic PH than cirrhosis, often triggered by complications of an abdominal operation. Data regarding management are limited to case series. No formal recommendations except for use of NSBB for CSPH can be suggested to prevent initial hemorrhage.

Guidance statements:

40. Patients with gastric or ectopic varices have CSPH and therefore the use of NSBBs should be considered for prevention of rebleeding and decompensation. These patients should be investigated for the presence of portal vein thrombosis.
41. Patients with high-risk cardiofundal (GOV2 or IGV1) varices (≥10 mm, red wale signs, CTP class B/C) who have contraindications or intolerance to NSBBs may be considered for primary prophylaxis with endoscopic cyanoacrylate injection (ECI).

42. Neither TIPS nor BRTO (or related obliterative techniques) are recommended to prevent first hemorrhage in patients with fundal varices that have not bled.

6.2 Management of initial and recurrent bleeding

The initial management of acute gastric or ectopic variceal bleeding should follow the guidance for acute esophageal variceal bleeding (see **Section V.E** and **Figure 4**). Once endoscopy confirms the presence of bleeding cardiofundal or ectopic varices, the next management steps will be determined by center expertise and the patient's vascular anatomy based on cross-sectional imaging. If local expertise in the management of bleeding GV is not available, the patient should be referred to a tertiary care center. If the initial control of bleeding is not achieved, balloon tamponade preferentially using the Linton-Nachlas or gastric balloon of the Minnesota tube can be used as a bridge to definite therapy. Various endoscopic and endovascular options are available including ECI, endoscopic cyanoacrylate with endoscopic coiling, endoscopic band ligation, BRTO (including variants such as mBRTO, balloon-occluded antegrade transvenous obliteration, and PARTO), and TIPS; please refer to the recent AASLD Practice Guidance related to TIPS and endovascular therapy for variceal hemorrhage for detailed descriptions of technical aspects and risks of these approaches.[212] Multidisciplinary (hepatology, interventional endoscopy, interventional radiology) assessment and management of patients is recommended.

Endoscopic adhesive glue injection, most commonly using cyanoacrylate (ECI) (not FDA approved in the United States for this indication) and often augmented with coil embolization, can achieve effective results for initial hemostasis[213–216] with success rates as high as 87%–100%, mostly in small series (Supplemental Table 2, http://links.lww.com/HEP/I69). EVL is a therapeutic option with low/moderate rates of bleeding control (45%–93%)[214,215]; however, rebleeding rates are higher with EVL compared with glue.[217] Thus, EVL should only be performed if no other options are readily available and if the site of rupture (high-risk red signs or platelet plug) is visualized and the varices can be completely suctioned into the banding cap. Use of balloon occlusion retrograde transvenous variceal obliteration and related endovascular approaches (e.g., BRTO, balloon-occluded antegrade transvenous obliteration, coil-assisted retrograde transvenous obliteration, etc.; please refer to Abraldes et al[212] for details of these

techniques), in which portosystemic collaterals are occluded angiographically through spontaneous splenorenal (or similar) shunts, has shown to be a successful approach in case series for management of acute cardiofundal variceal bleeding.[216] However, BRTO and similar obliterative therapies can be associated with an increased incidence of ascites and bleeding from esophageal varices,[211] although in others, obliterative therapy will improve liver function and reduce encephalopathy by redirecting portal flow toward the liver. The selection between TIPS or obliterative therapy should be based on patient characteristics and local expertise.[211] TIPS may be preferred with preserved liver function (MELD-sodium [MELDNa] < 20) in the presence of large esophageal varices, significant ascites, and portal vein thrombosis and the absence of HE. BRTO may be preferred in patients with HE, MELDNa > 20, or Freiburg Index of Post-TIPS Survival (FIPS) > 0.92.[218–220] Anatomic considerations may also guide the choice of TIPS versus retrograde transvenous obliteration.[212]

In the event that bleeding cannot be initially controlled with medical therapy, EVL, glue and/or transvenous obliteration, salvage TIPS creation is highly effective for initial bleed control with over 90% success rate in non-prehepatic PH[221] at the cost of increased risks of HE and hepatic functional decline associated with this procedure. Once initial bleeding control is achieved, management follows the same rules as for esophageal varices. Patients with CTP score 7–13 points with active bleeding on endoscopy can be considered for preemptive TIPS creation,[173] even in the setting of acute-on-chronic liver failure[42]; it should be noted, however, that the initial trials of preemptive TIPS only included patients with esophageal varices[173] and the specific role of preemptive TIPS in gastric and ectopic varices has only being studied in an RCT so far with findings quite similar to those of early TIPS for esophageal varices. Because patients with GV typically bleed at lower pressures and the GV system can compete with the portal vein for blood flow,[202] TIPS placement for gastric or ectopic varices should be accompanied by simultaneous collateral obliteration or embolization.[212,222] See a suggested management algorithm (**Figure 4**) for bleeding GV management; please refer to Abraldes et al[212] for details of these techniques.

Data around the prevention of rebleeding cardiofundal or ectopic varices are limited to small randomized trials and prospective single center cohorts. Overall rebleeding rates range from

<10% to as high as 54%.[223–231] Similar to esophageal variceal bleeding, a combination of a local therapy (endoscopic or endovascular) and portal pressure reduction with NSBB are recommended, although the beneficial effects of NSBB in the setting of secondary prophylaxis of rebleeding of GV have not been specifically studied[29]; NSBB are not required after TIPS placement if portosystemic gradient is reduced to under 12 mm Hg. Several endoscopic or endovascular options are available for prevention of rebleeding, and the decision should be taken on a case-by-case basis in a multidisciplinary setting depending on the characteristics of the patient and local expertise[212] and per recent AASLD guidance.[212] ECI with or without endoscopic ultrasound guidance and with or without concomitant use of coils has been shown to be effective on prevention of rebleeding.[214,227,228,231–236] It has been suggested to repeat ECI every 2–4 weeks until obliteration. After initial obliteration, repeat surveillance endoscopy should be performed within 3–6 months and thereafter annually.[198] Use of transvenous obliteration (BRTO and technical variants) has demonstrated lower rebleeding rates, fewer hospitalizations, and lower cost compared with ECI in a recently published RCT that included 64 patients with cirrhosis; however, no survival benefit was observed.[227] A meta-analysis of observational studies suggests that BRTO is associated with lower rebleeding rates than TIPS at least in limited follow-up.[237] Importantly, patients who underwent transvenous obliteration had significantly less encephalopathy than those with TIPS creation.[237,238] Because of the advantage of TIPS in terms of ascites control, the best use of retrograde transvenous obliteration alone (without concurrent TIPS) is for control of bleeding or prevention of rebleeding in patients with gastric or ectopic varices because of prehepatic PH, because these patients usually do not develop ascites.[237,239,240] TIPS creation is associated with comparable or lower rebleeding rates than ECI but with higher rates of HE and similar survival outcomes.[229,241] Concurrent variceal obliteration at the time of TIPS creation further reduces the risk of rebleeding as well as decreasing the risk of HE.[222,229,237,238,241,242] Finally, a special consideration applies to patients with gastric and ectopic varices as a consequence of isolated splenic vein thrombosis. In these cases of "left-sided portal hypertension," splenectomy, splenic vein stenting,[243] and splenic artery embolization[244] should be considered.

Bleeding and prevention of rebleeding from ectopic varices should be managed similarly to esophageal and gastric varices. Data for clear beneficial approaches for these rare cases remain

limited to small retrospective cohorts.[208,245–247] Endoscopic therapy can be effective, and several reports have shown adequate bleeding control when using endovascular embolization of the feeding vessel with or without a TIPS.[248–254]

Guidance statements:

43. Initial management of bleeding gastric or ectopic varices should be identical to the management of bleeding esophageal varices, including vasoactive therapy, antimicrobials, conservative transfusion strategy, and endoscopic evaluation, within 12 hours.
44. Patients with bleeding gastric or ectopic varices should have contrast-enhanced cross-sectional imaging to define the anatomy of portosystemic collaterals or presence of venous thrombosis that would guide therapy.
45. In patients with acute hemorrhage from gastric (GOV2/IGV1) or ectopic varices, either endoscopic cyanoacrylate therapy, TIPS, or retrograde transvenous variceal embolization/obliteration can be considered first-line options. Retrograde obliteration is preferred when TIPS is contraindicated.
46. In patients who underwent ECI as the main therapy, the addition of NSBBs is recommended to prevent rebleeding, in absence of contraindications. Additionally, repeat endoscopic treatment at intervals every 2–4 weeks until obliteration and long-term surveillance should be performed.
47. Patients with bleeding GV caused by isolated splenic vein thrombosis should be evaluated for splenectomy, splenic vein stenting, or splenic artery embolization.

7 ADDITIONAL TOPIC AREAS FOR GUIDANCE

7.1 Portal gastropathy

PHG and/or portal enteropathy, characterized by a "snake-skin" mosaic mucosal pattern with variable degrees of intraepithelial hemorrhage, is a common endoscopic observation in cirrhosis. The condition results from increased portal pressure and submucosal vascular hyperemia resulting in associated mucosal venous and capillary ectasia.[255,256] Several clinical grading systems have been proposed to identify features associated with high or low risk of complications, including the New Italian Endoscopic Club (NIEC) and Baveno III systems[257,258]

(**Table 6**). Consensus among grading systems is 1) that the presence of intramucosal hemorrhage (cherry red spots, black-brown spots, or red point lesions) differentiates severe from mild PHG with moderate correlation with clinical events during follow-up and 2) that concomitant gastric antral vascular ectastia (GAVE) confers higher risk of hemorrhage. The prevalence of PHG among patients with compensated cirrhosis ranges from 49% to 80%,[259–261] with lower prevalence in patients without varices (11%)[262] or small varices (35%)[262] relative to those with medium or large varices (80%–97%).[261] The development of PHG usually requires the presence of CSPH.[263,264] During longitudinal follow-up of patients with cirrhosis, progression of PHG is frequently, and regression more rarely, observed. For instance, in the HALT-C study, 97/170 (57%) patients with cirrhosis without PHG at baseline developed PHG, and 115/174 (66%) with baseline PHG exhibited worsening grade over 4 years of clinical follow-up[265]; the presence of varices and/or CTP class B/C cirrhosis are the strongest predictors of progression.[259,261,262] Additionally, worsening of PHG features can be observed transiently after sclerotherapy or ligation of esophageal varices,[266,267] correlating with poorer clinical outcomes.[259]

The primary sequelae of PHG are acute and chronic hemorrhage. Acute bleeding from PHG is uncommon, occurring in 2.5%–5%[259,261,262] of cases. Although spontaneous cessation occurs in over half of cases with supportive care, low quality data support the use of intravenous octreotide, somatostatin, or terlipressin as a safe initial therapy to accelerate resolution and reduce need for transfusion.[268,269] Acute administration of NSBBs reduces gastric hyperemia[270,271] and may also attenuate bleeding in acute PHG hemorrhage.[272] Most prospective studies suggest a potential prophylactic role for reduction of first or recurrent acute bleeding from PHG with NSBBs[267,272–275] after exclusion of *Helicobacter pylori* as an alternative cause of mucosal granularity.[276]

Chronic blood loss, typically defined as a 2 g/dL reduction in hemoglobin over a 6-month interval, occurs more commonly than acute bleeding, present in up to 4%–12% of cases.[262,277] An RCT showed a clear benefit from propranolol in preventing recurrent bleeding from PHG[275]. Recent nonrandomized data suggest that argon plasma coagulation may also attenuate chronic blood loss with chronic PHG bleeding.[278–280] A small cases series documented some response to PHG versus GAVE-related acute bleeding with hemostatic spray.[281] To be expected, case series

of portocaval shunts[282] and TIPS[283] suggest high rates of bleeding control with portosystemic decompression.

PH-related polyps can be found in the gastric antrum and occasionally in the duodenum in approximately 1%–10% of patients with cirrhosis, are predominantly hyperplastic, and carry negligible risk of malignant transformation.[284,285] PH-related polyps can contribute to chronic gastrointestinal bleeding in patients with cirrhosis, which may respond to NSBB or TIPS. Routine biopsy of PH-related polyps should be discouraged because of the benign nature and risk of significant bleeding from feeding vessels deep within the submucosa.

Guidance statements:

48. Patients with greater than mild PHG should be presumed to have CSPH and should therefore be considered for prophylactic NSBB to prevent decompensation; this intervention may also prevent hemorrhagic complications or iron-deficiency anemia from severe PHG.
49. In acute bleeding from severe PHG, vasoactive therapy (e.g., somatostatin, somatostatin analogs such as octreotide, or terlipressin if available; see **Table 5**) for 2–5 days at doses used for variceal bleeding should be considered.
50. NSBB are recommended to prevent rebleeding from PHG and PH-related polyps.
51. If bleeding from PHG becomes transfusion-dependent despite NSBB, TIPS placement should be considered.

7.2 Varices in HCC

Gastrointestinal bleeding is a known complication of anti–vascular endothelial growth factor therapies, including bevacizumab[286] and tyrosine kinase inhibitors.[287] Variceal hemorrhage is an infrequent complication[288] but in most (but not all) series appears to be increased in the presence of portal vein thrombosis.[288–290] Although recent pivotal trials for medications with anti–vascular endothelial growth factor properties for advanced HCC have required endoscopy within 6 months of enrollment to identify and treat high-risk varices,[291,292] recent data suggest a poor correlation between endoscopic findings and variceal bleeding and no benefit of EBL over NSBB prophylaxis.[288] Among patients with acute variceal bleeding in HCC, rebleeding rates

are increased relative to patients without HCC but secondary prophylaxis does significantly reduce this risk.[293]

Recommendation:

52. Prevention and treatment of AVH and hepatic decompensation in patients with HCC should follow the same principles as those for patients without HCC.
53. In the absence of contraindications, NSBB therapy is recommended for the primary prophylaxis for VH and prevention of decompensation in patients with HCC with CSPH (including varices).
54. In the presence of occlusive bland or malignant PVT, upper endoscopy is recommended to investigate the presence of gastroesophageal varices. If varices are detected, NSBB or endoscopic band ligation are recommended; preference is given to NSBB (including carvedilol) because of benefits beyond prevention of variceal hemorrhage.

7.3 PH in pregnancy

Few data exist to guide systematic recommendations regarding the management of varices in cirrhotic PH in pregnancy. AASLD guidance recommends that all patients with cirrhosis or noncirrhotic PH planning pregnancy undergo upper endoscopy within 1 year of conception[294]; unscreened patients should undergo EGD early in the second trimester. Primary prophylaxis with NSBB or EBL for medium and large varices are recommended in pregnant patients with preference for EBL in the presence of cherry red spots or red wale signs.[294] In the setting of AVH, terlipressin should be avoided because of stimulation of uterine contraction, but somatostatin or octreotide may be used. Case series exist documenting utilization of band ligation[295] and TIPS[296] for secondary prophylaxis or to control refractory variceal hemorrhage in pregnancy. Weak evidence suggests that carvedilol results in lesser fetal growth retardation in pregnancy relative to propranolol when used for cardiac indications.[297]

55. All patients with cirrhosis or noncirrhotic PH planning pregnancy should undergo upper endoscopy within 1 year of conception.
56. Unscreened pregnant patients with cirrhosis or noncirrhotic PH should undergo EGD early in the second trimester.

7.4 Endoscopy before TEE

There is no evidence that TEE in patients with varices poses a significant risk of inducing variceal hemorrhage or that routine upper endoscopy prior to TEE significantly impacts patient outcomes.[298–300] As such, routine upper endoscopy prior to TEE is not recommended.

Guidance statement:

57. Routine upper endoscopy prior to TEE in patients with cirrhosis is not recommended.

7.5 Preoperative TIPS prior to nonhepatic operation

Few data, and none emerging from RCTs, exist to confirm a benefit or risk-stratify patients with PH who may benefit from preoperative TIPS for elective nonhepatic operation. A retrospective propensity-matched study including a small number of patients with preoperative TIPS undergoing visceral and nonvisceral operation identified a reduction of acute-on-chronic liver failure and death within 90 days of operation.[301] In the absence of prospective studies, TIPS can be considered in patients on a case-by-case basis weighing the potential surgical benefits of TIPS with potential increased risk of HE and of worsening liver failure.

Guidance statement:

58. Preoperative TIPS can be considered on a case-by-case basis after careful consideration of potential surgical benefits relative to potential harms related to the procedure (encephalopathy, worsening of liver failure).

8 CONCLUSIONS AND AREAS FOR FUTURE RESEARCH (BOX 4)

The ability to noninvasively identify patients at high risk for decompensation and evidence that decompensation rates can be decreased with therapy enable a paradigm shift toward prevention of decompensation through NSBBs, disease control, and lifestyle modification. Once decompensated, improved understanding of resuscitation and the role of preemptive TIPS should improve the survival of patients with AVH. It is expected that advances in knowledge on the mechanisms involved in increased hepatic vascular tone and disease progression/regression will result soon in RCTs of new drugs for PH in patients with cirrhosis.

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BOX 1 What's new

Recognition of the concept of compensated advanced chronic liver disease (cACLD), a shift away from the requirement of a histological or radiological diagnosis of cirrhosis for initial patient risk stratification
Codification of methodology to use noninvasive assessments to identify clinically significant portal hypertension (CSPH)
Endorsement of a change in paradigm with the recommendation of early utilization of nonselective beta-blocker therapy when CSPH is identified in order to decrease the risk of cirrhosis decompensation
Updated guidance on the use blood and blood products during initial resuscitation of acute variceal hemorrhage
Endorsement of preemptive TIPS in select patient subsets
Guidance on the use of upper endoscopy prior to transesophageal echocardiography

BOX 2 ABCs of HVPG measurement

1. Consider the planned approach:

Approach	Pros	Cons	Comments
Transjugular	Fast, allows biopsy	Potential for arrythmia	Preferred at most centers
Transfemoral	No risk of arrythmia	Not adequate to obtain biopsy	
Antecubital	Less invasive	Potential for arrythmia, unable to biopsy	Rarely used

2. Select scale range to be 0–40 or 0–50 mm Hg. Adjust 1 grid mark = 1 mm Hg whenever possible and select low recording speed (1–7.5 mm/s).

3. Use precalibrated transducers connected to a monitoring system with printing capacity or digital format that can be saved. Put transducer level at midaxillary line.

4. Use balloon-tipped catheters of 10–12 mm balloon diameter.

5. Print calibration scale and zero level before any hemodynamic measurement.

6. Measurements should be obtained in a quiet ambience, asking the patient to breathe quietly and not to move or speak during measurements. Patients should not be breathing deeply/snoring during measurements to avoid respiratory artifacts.

7. Do not use deep sedation (avoid fentanyl and propofol). Midazolam at low dose (0.02 mg/kg) is acceptable.

8. FHVP should be measured with the tip of the catheter 2–4 cm inside the hepatic vein. WHVP (after balloon inflation) should be obtained at the same place, or more distally (if the vein is too large to be occluded by the balloon), after checking that there is no reflux of contrast around the balloon or through another hepatic vein. Rinse the catheter thoroughly before measurements.

9. Run pressure measurements for 15–20 s for FHVP and for at least 1 min for WHVP because it may take a long time to stabilize. WHVP should be read when stable, on the last 20–30 s.

10. Label each measurement. Discard measurements in which there are artifacts caused by moving, coughing, snoring, or speaking.

11. Run all measurements in triplicate. Sequential measurements should be within 2 mm Hg of the immediately prior measurement. Greater variability should prompt reassessment of technique.

12. In addition to WHVP and FHVP, obtain measurements of the FHVP with the tip of the catheter 1–2 cm from the hepatic vein outlet into the IVC. Obtain also the IVC pressure at the level of the hepatic vein outlet (close to the right atrium) and of the right atrial pressure. FHVP and IVC pressure should be almost identical; if the FHVP exceeds > 2 mm Hg the IVC, obtain a venography to rule out any obstruction.
Abbreviations: FHVP, free hepatic vein pressure; IVC, inferior vena cava; WHVP, wedged hepatic vein pressure.

BOX 3 Contraindications to nonselective beta-blockers

Absolute contraindications
Asthma
2nd and 3rd degree atrioventricular block (in absence of implanted pacemaker)
Sick sinus syndrome
Extreme bradycardia (<50 bpm)
Relative contraindications
Psoriasis
Periphery arterial disease
Chronic obstructive pulmonary disease
Pulmonary artery hypertension (controversial)
Insulin-dependent diabetes mellitus (interferes with symptoms of hypoglycemia)
Raynaud syndrome

BOX 4 Key areas of future research

(a) Prospective validation of the "rule of 5" for the noninvasive selection of candidates for early initiation of nonselective beta-blockers (NSBBs) to prevent clinical decompensation and avoid screening endoscopy

(b) Systematic and cross-platform validation of cutpoints for magnetic resonance elastography, two-dimensional shear wave elastography, and point shear wave elastography for estimation of presence of clinically significant portal hypertension and high-risk varices

(c) Identification and validation of noninvasive modalities to monitor 10%–20% changes in HVPG

(d) Confirmation of clinical, Noninvasive Liver Disease Assessment (NILDA), and/or HVPG thresholds for clinical recompensation after which screening endoscopy or NSBB therapy is no longer required, allowing de-escalation of monitoring and treatment for portal hypertension

(e) External validation of the PREDESCI trial in additional populations (patients with NASH)

(f) Definition of patients with portal hypertension who might benefit from an earlier decision for TIPS (i.e., after first bleeding; before major operation)

(g) Quantification of the benefit from nutritional intervention in patients with cirrhosis and sarcopenia and/or frailty for prevention of first or further decompensation and/or improvement in survival

(h) Confirmation of the safety and effectiveness of statins in improving survival and/or preventing decompensation, further decompensation, and acute-on-chronic liver failure when used alone or coadministered with NSBBs, rifaximin, or other treatments

(i) Larger prospective studies of self-expanding esophageal stents to confirm role and refine utilization in acute variceal hemorrhage

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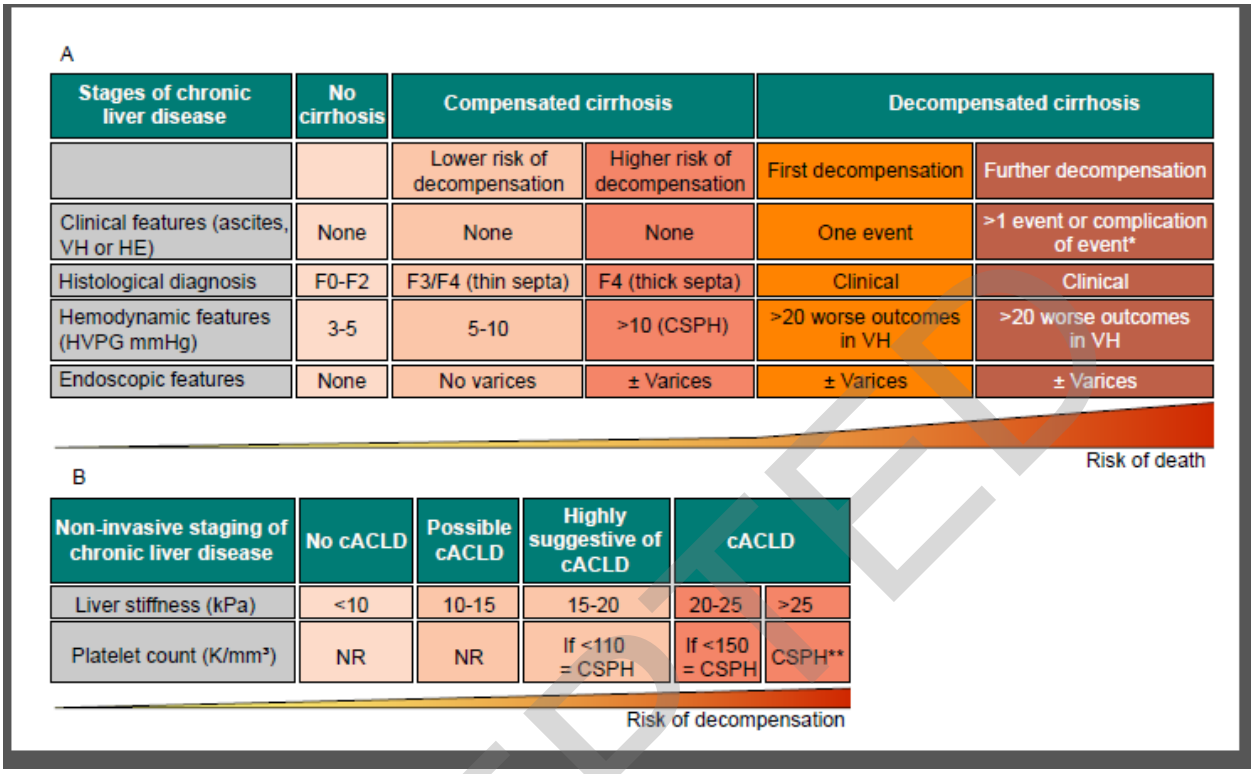

A

Stages of chronic liver disease	No cirrhosis	Compensated cirrhosis		Decompensated cirrhosis	
		Lower risk of decompensation	Higher risk of decompensation	First decompensation	Further decompensation
Clinical features (ascites, VH or HE)	None	None	None	One event	>1 event or complication of event*
Histological diagnosis	F0-F2	F3/F4 (thin septa)	F4 (thick septa)	Clinical	Clinical
Hemodynamic features (HVPG mmHg)	3-5	5-10	>10 (CSPH)	>20 worse outcomes in VH	>20 worse outcomes in VH
Endoscopic features	None	No varices	± Varices	± Varices	± Varices

Risk of death

B

Non-invasive staging of chronic liver disease	No cACLD	Possible cACLD	Highly suggestive of cACLD	cACLD	
Liver stiffness (kPa)	<10	10-15	15-20	20-25	>25
Platelet count (K/mm³)	NR	NR	If <110 = CSPH	If <150 = CSPH	CSPH**

Risk of decompensation

Figure 1. The stages of cirrhosis and advanced chronic liver disease. (A) Clinical features, histologic findings, hepatic venous pressure gradients (HVPG), and endoscopic features typical of compensated cirrhosis with and without clinically significant portal hypertension (CSPH), decompensated cirrhosis, and further decompensated cirrhosis. Relative risk of death is indicated in the purple dashed line. (B) Liver stiffness measurements and platelet counts used to characterize compensated advanced chronic liver disease (cACLD) and CSPH using noninvasive, nonhistological criteria. HE, hepatic encephalopathy; VH, variceal hemorrhage.

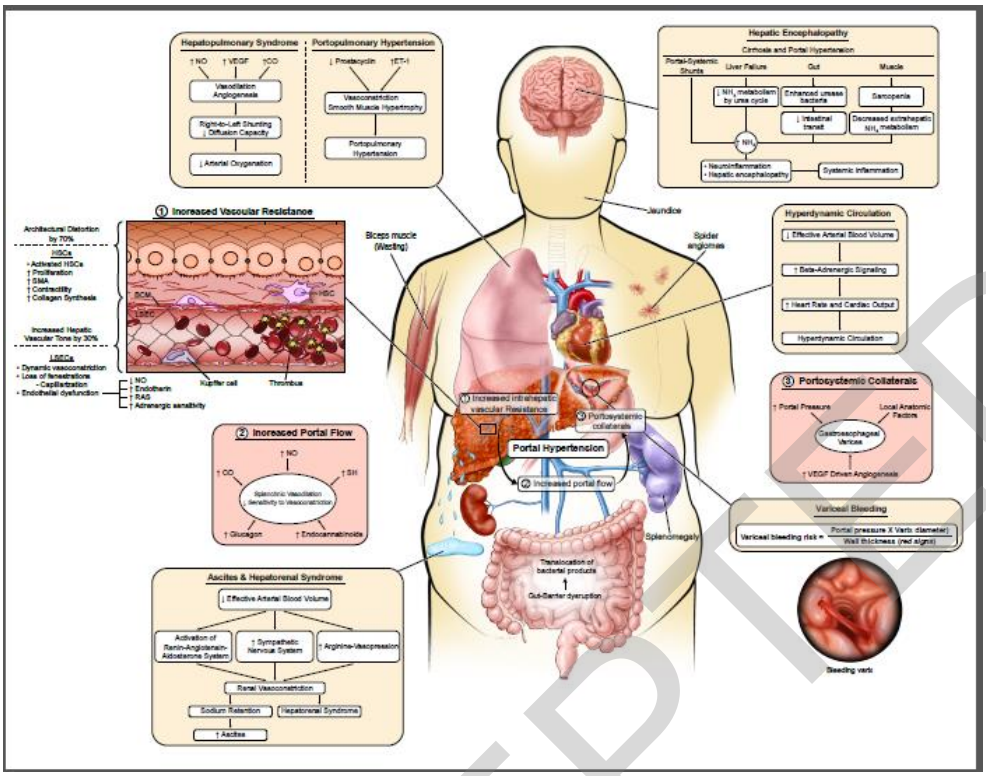

Figure 2. Pathophysiology of portal hypertension and related complications. Portal hypertension results from a series of maladaptive responses to chronic liver injury and cirrhosis. Initially, structural mechanisms because of accumulation of fibrous tissue, regenerative nodules, microthrombi, parenchymal extinction, and collapse lead to an increase in intrahepatic vascular resistance (1). In addition to architectural distortion, dynamic sinusoidal vasoconstriction contributes to 30% of the total increase in vascular tone. These structural changes lead to an increased portal pressure gradient; when this reaches values of about 10 mm Hg, it gives rise to formation of portal-systemic collaterals and compensatory splanchnic vasodilation, which, in turn, increases portal blood flow and, consequently, portal pressure (2). One of the first consequences of portal hypertension is the development of portosystemic collaterals, for which vascular endothelial growth factor (VEGF)-driven angiogenesis plays an important role (3). Gastroesophageal varices represent the most clinically relevant collaterals because of their increased risk of bleeding. Bleeding is directly dependent on increased wall tension at the varices, determined by portal pressure, variceal diameter, and thin wall thickness. Vasodilation occurs also in the systemic circulation resulting in a hyperdynamic circulatory state, driven by decreased effective arterial blood volume leading to activation of neurohumoral and

vasoconstrictive systems, sodium and water retention, and increased cardiac output. This process eventually results in the development of ascites and, at late stages, hepatorenal syndrome because of compensatory renal vasoconstriction. Hepatic encephalopathy represents a multifactorial complication of portal hypertension, resulting from portosystemic shunting, impaired synthetic liver function, increased bacterial translocation, and muscle wasting (sarcopenia). Finally, imbalances on vasoconstrictors and vasodilators in the pulmonary circulation results in hepatopulmonary syndrome (increased vasodilation) and portopulmonary hypertension (increased vasoconstriction). CO, carbon monoxide; H_2S, hydrogen sulfide; HVR, hepatic vascular resistance; NO, nitric oxide. ET: endothelin;

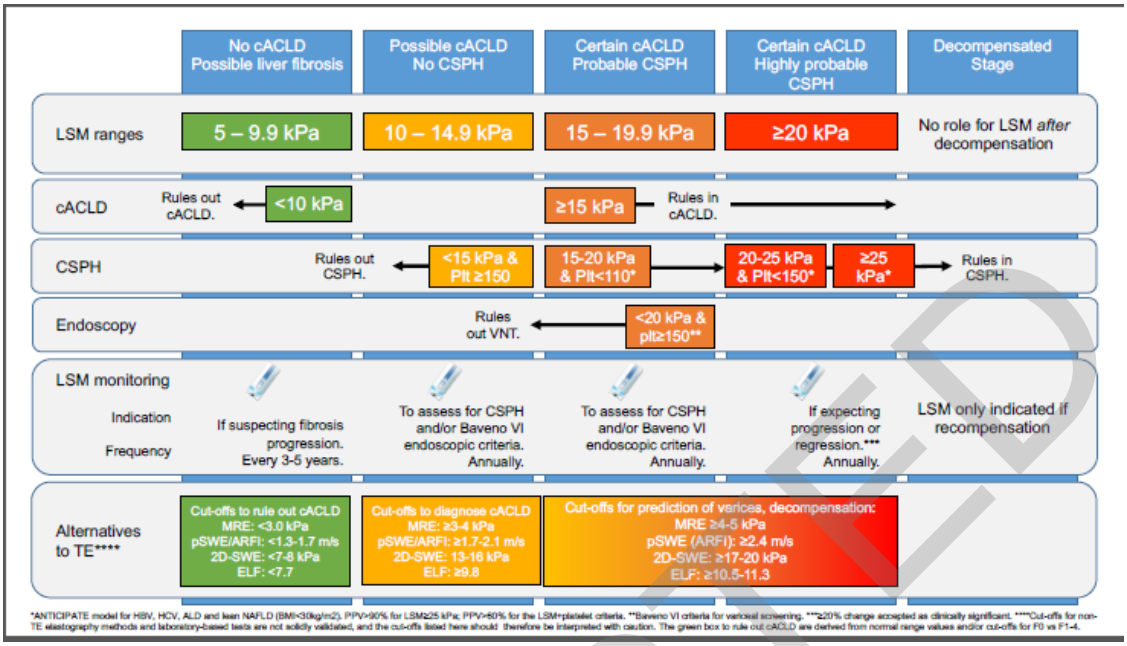

Figure 3. The use of noninvasive tests to stage and managed advanced chronic liver disease. Schema for using liver stiffness measurement (LSM) by transient elastography to stage advanced chronic liver disease (ACLD), identify clinically significant portal hypertension (CSPH), the stage-specific role of upper endoscopy to identify varices needing treatment (VNT), serial monitoring, and alternative approaches. *ANTICIPATE model for HBV, HCV, alcohol-associated liver disease, and lean NAFLD (body mass index < 30 kg/m^2). Positive predictive value (PPV) > 90% for LSM ≥ 25 kPa; PPV > 60% for the LSM + platelet criteria. **Baveno VI criteria for variceal screening. ***≥20% change accepted as clinically significant. ****Cutoffs for non-TE elastography methods and laboratory-based tests are not solidly validated, and the cutoffs listed here should therefore be interpreted with caution. The green box to rule out compensated ACLD (cACLD) are derived from normal range values and/or cutoffs for F0 vs. F1–4. 2D-SWE, two-dimensional shear wave elastography; ARFI; Acoustic Radiation Force Impulse Imaging;

BMI, body mass index; ELF, enhanced liver fibrosis; MRE, magnetic resonance elastography; Plt: platelet count; TE: transient elastography.

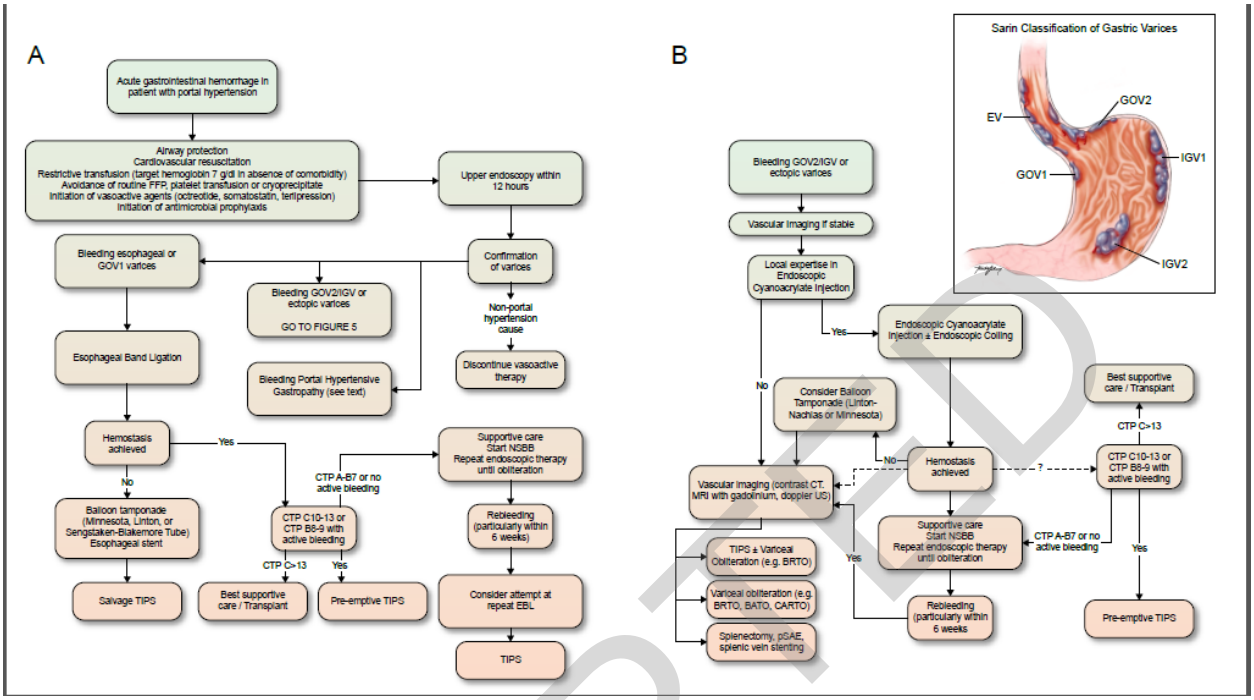

Figure 4. Management of acute variceal bleeding. Initial management of a patient with upper gastrointestinal bleeding that could be variceal in origin includes routine cardiopulmonary resuscitation, a conservative strategy for red cell transfusion, avoidance of routine fresh frozen plasma (FFP) and cryoprecipitate, prompt initiation of vasoactive therapy and antimicrobial prophylaxis. Upper endoscopy is recommended within 12 hours with specific pathways provided for (A) esophageal and/or GOV1 bleeding, (B) GOV2/IGV2 or ectopic varices, and nonvariceal causes. BATO, balloon-occluded antegrade transvenous obliteration; BRTO, balloon-occluded retrograde transvenous obliteration; CARTO, coil-assisted retrograde transvenous obliteration; CTP, Child-Turcotte-Pugh; NSBB, nonselective beta-blocker; pSAE: procedure related Serious Adverse Event; US, ultrasound.

TABLE 1 Classification of portal hypertension.

Classification	Level	Examples
Prehepatic	Portal vein and branches	Portal vein thrombosis
Intrahepatic	Presinusoidal (portal triads)	Schistosomiasis, primary biliary cholangitis, sarcoidosis, portosinusoidal vascular disorder
	Sinusoidal	Cirrhosis (all causes), alcohol-associated hepatitis
	Postsinusoidal (central veins)	Sinusodial obstruction syndrome
Posthepatic	Hepatic veins, inferior vena cava	Budd-Chiari syndrome, congestive hepatopathy (multiple causes including but not limited to pulmonary hypertension, heart failure, constrictive pericarditis)

TABLE 2 Therapeutic targets in portal hypertension.

Target	Treatments
Cirrhosis	
Etiological therapy	Antiviral therapy (HCV, HBV), immunosuppression (AIH), alcohol abstinence and relapse prevention therapy
Healthy lifestyle	Alcohol elimination Regular moderate aerobic exercise Maintenance of body weight at body mass index 18–29 kg/m^2 Adequate protein intake (>1 g/kg per day), avoidance of processed foods, avoidance of sugar and high-fructose corn syrup–sweetened food products, avoidance of salty foods, tobacco avoidance High-protein nocturnal snack
Increased hepatic vascular resistance	TIPS Carvedilol
Activated HSC	Antifibrotic agents (experimental), anticoagulants
LSEC dedifferentiation	Statins
Hepatocyte injury	Antioxidants
Splanchnic vasodilation	Nonselective beta-blockers and carvedilol Terlipressin Somatostatin and analogs
Gut-liver axis	Nonselective beta-blockers and carvedilol Fecal transplantation, probiotics, antibiotics
Collaterals and varices	Nonselective beta-blockers and carvedilol Antiangiogenics (experimental) Endoscopic therapy Collateral embolization, BRTO, PARTO,esophageal stents, balloon tamponade

Abbreviations: AIH, autoimmune hepatitis; BRTO, balloon-occluded retrograde transvenous obliteration. PARTO: plug occluded retrograde transvenous obliteration

TABLE 3 Nonselective beta-blockers used in portal hypertension.

Therapy	Mechanism of action	Starting dose	Titration	Maximal dose	Goal	Common adverse effects	Maintenance
Propranolol	Decreased cardiac output; caused by decreased heart rate and contractility from beta-1 adrenergic blockade, plus	20–40 mg twice daily	Increase the dose every 2–3 days until treatment goal	Without ascites: 320 mg/day; with ascites: 160 mg/day	HR of 55–60 bpm if tolerated; SBP should be maintained ≥90 mm Hg	Fatigue, bradycardia, dyspnea, orthostasis, hypotension, constipation	Indefinitely or until TIPS or liver transplant. No indication for routine upper endoscopy
Nadolol	Splanchnic arterial vasoconstriction; caused by beta-2 blockade leading to unopposed alfa-adrenergic vasoconstriction	20–40 mg at bedtime		Without ascites: 160 mg/day; with ascites: 80 mg/day			

Carvedilol	Above plus decreased intrahepatic vascular resistance; caused by anti-alpha-adrenergic activity	6.25 mg once daily	Increase to 6.25 mg twice daily after 3 days	12.5 mg/day (higher doses could be considered for nonhepatic indications)	No HR goal; SBP should be maintained ≥90 mm Hg

Abbreviations: SBP: spontaneous bacterial peritonitis; HR: heart rate

TABLE 4 Selection of ongoing clinical trials for novel pharmacological agents to prevent or treat portal hypertension.

Class	Agent	Ph	Duration	Key inclusion criterion	Outcome(s)	*N*	Country	NCT	Status
Anticoagulant	Rivaroxaban	3	24 months	Compensated cirrhosis with CSPH (clinical or HVPG)	Hepatic decompensation	160	Spain	NCT02643212 (CIRROXABAN)	Unknown
	Rivaroxaban	1	12 hours	CTP A/B cirrhosis	Pharmacological	24	Switzerland	NCT04874428	Recruiting
Anti-inflammatory	Belapectin	2/3	18 months	NASH cirrhosis	New varices	1,010	United States	NCT04365868 (NAVIGATE)	Recruiting
Microbiome	Rifaximin	3	60 days	Compensated cirrhosis	Change in HVPG	60	Italy	NCT02508623 (ERASE)	Unknown

				with CSPH (HVPG)				
	Atorvastatin	4	18 months	Compensated cirrhosis with CSPH (HVPG)	Death, LT, hospitalizations	162	Denmark	NCT04072601 (STATLiver)	Recruiting (16)
Statin	Rosuvastatin	2/3	2 months	Carvedilol-treated CSPH, incomplete response	Change in HVPG	80	Brazil	NCT03720067	Recruiting
	Simvastatin	3	24 months	Compensated cirrhosis with CSPH (clinical)	Hepatic decompensation or HCC	500	United States[a]	NCT03654053 (SACRED)	Recruiting (14)

	Simvastatin ± rifaximin	3	12 months	Decompensated cirrhosis	Incidence of ACLF	240	Europe	NCT03780673 (LiverHOPE)	Recruiting (15)
Unknown	Berberine	3	12 months	HBV cirrhosis with VNT on carvedilol	Progression of varices	288	China	NCT04543643	Not yet recruiting
Vasodilator	BI 685509	2	24 weeks	Compensated cirrhosis with CSPH (HVPG)	Change in HVPG	150	TBD	NCT05161481	Not yet recruiting

[a]A National Institutes of Health–sponsored multicenter trial also planned in the United States.

ACLF, acute-on-chronic liver failure; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh; NCT, National Clinical Trial; TBD, to be determined; VNT, varices needing treatment.

TABLE 5 Vasoactive agents for acute variceal bleeding.

Agent	Dosing	Duration
Octreotide	Initial i.v. bolus of 50 mcg and continue infusion at a rate of 25–50 mcg/hour[302–304]	2–5 days
Somatostatin	Initial i.v. bolus of 250 mcg and continue infusion at a rate of 250–500 mcg/hour[305,306]	2–5 days
Terlipressin[a]	Initial 24–48 hours: 2 mg i.v. every 4–6 hours and then 1 mg i.v. every 4–6 hours[305,307–309]	2–5 days

[a]Not approved for this indication in North America.

References: Garcia-Tsao et al. *Hepatology*. January 2017[1]; Seo et al. *Hepatology*. September 2014.[152]

TABLE 6 Baveno III classification of portal hypertensive gastropathy.

Feature	**Score**
Mucosal mosaic pattern	
Mild	1
Severe	2
Red markings	
Isolated	1
Confluent	2
Gastric antral vascular ectasia (GAVE)	
Absent	1
Present	2

Note: Mild PHG ≤ 3, severe PHG ≥ 4.