

Practice Guidance



AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis

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 cardiopulmonary 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

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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.

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complications^[5] and vascular causes of PH.^[6] The present guidance is also meant to harmonize with the recently updated AASLD Practice Guidance on the use of TIPS, Variceal Embolization, and Retrograde Transvenous Obliteration in the Management of Variceal Hemorrhage.^[7] 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.

CONTEXT OF PH IN CIRRHOSIS

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.^[8] 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.^[9] 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.

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).^[10] 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.^[11]

Decompensation most commonly occurs when portal pressure gradients are at or exceed 10 mm Hg^[12–15] (measured by the hepatic venous pressure gradient described as follows). This pressure gradient defines “clinically significant portal hypertension” or CSPH.^[16] 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.”^[17]

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” (ACL D) 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 ACL D without prior decompensation is cACL D. LSM by transient elastography (TE) <10 kPa rules out cACL D and ≥15 kPa rules in cACL D.^[18–21] (The AASLD NILDA of Portal Hypertension does not advocate a specific cutpoint for LSM sufficient to rule in CSPH). LSM by TE can be further used to rule in CSPH at values >25 kPa (in patients who are not obese).^[22–24] 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.

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.^[9,15] 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.^[17,25] 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]

PATHOPHYSIOLOGICAL BASES OF PHARMACOLOGICAL THERAPY

Overview

In cirrhosis, the accumulation of fibrous tissue and nodule formation, with consequent vascular distortion, lead to an increase in intrahepatic vascular resistance and,

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)	Sinusoidal 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)

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.^[26] 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.

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^[27]).

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

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

(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/mm ³)	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.

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.^[28] 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,^[29,30] a trend for better tolerance, simpler administration, possibility of preventing ascites, and a potential survival advantage,^[31,32] carvedilol is the preferred NSBB for management of PH.

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.^[33–35] However, there are discrepant results on whether statins have additive effect with NSBB on HVPG reduction.^[33,36] 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)^[37] 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.^[38] 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.^[39] Presently, at least four prospective RCTs are testing physiological or clinical endpoints with statins in CTP A or B cirrhosis.^[38,40,41]

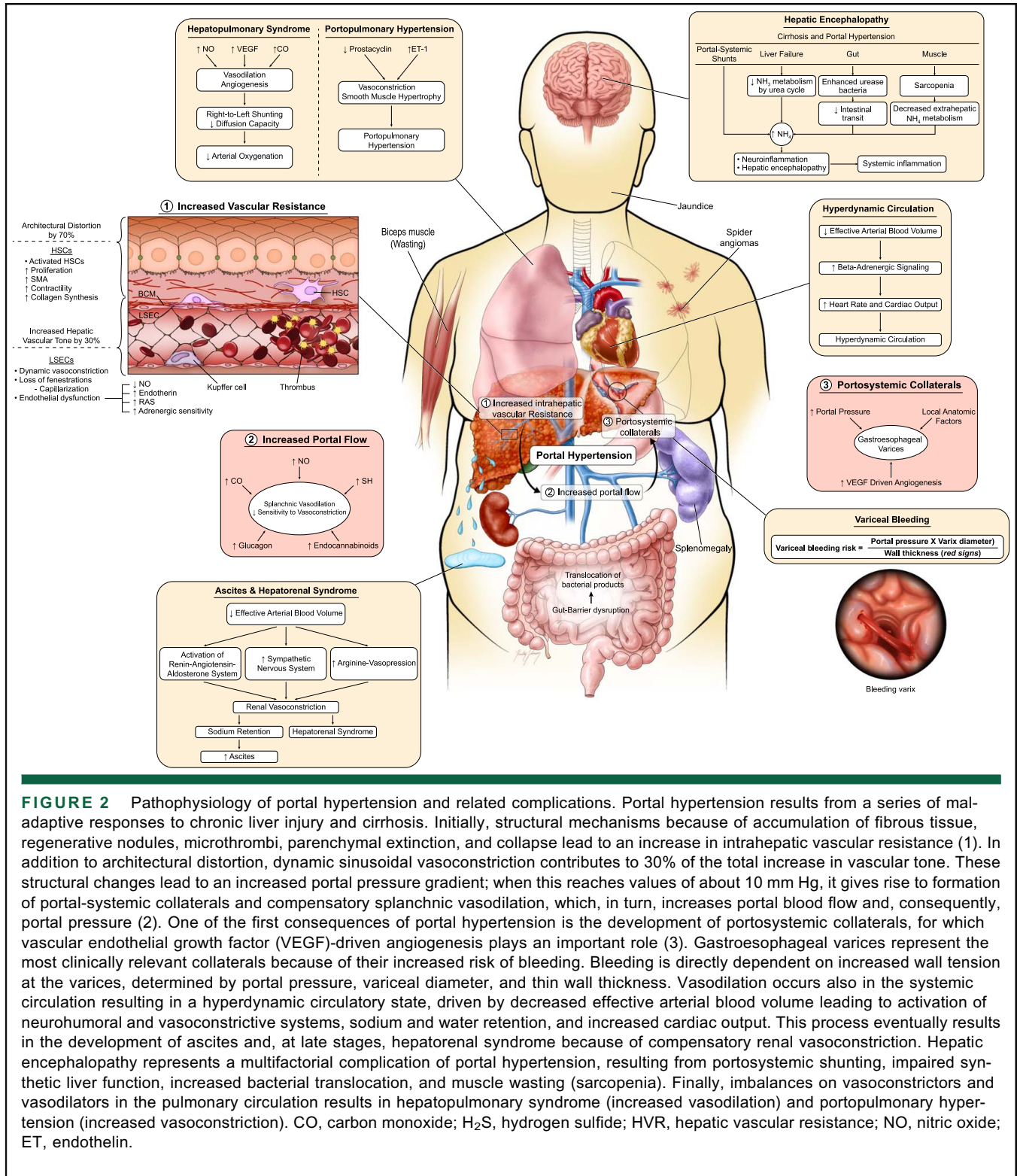


FIGURE 2 Pathophysiology of portal hypertension and related complications. Portal hypertension results from a series of maladaptive responses to chronic liver injury and cirrhosis. Initially, structural mechanisms because of accumulation of fibrous tissue, regenerative nodules, microthrombi, parenchymal 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; H₂S, hydrogen sulfide; HVR, hepatic vascular resistance; NO, nitric oxide; ET, endothelin.

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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.

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. Maintenance dosage can be given as a single daily dose or divided twice daily. In patients with concomitant arterial hypertension or cardiac disease, the dose of carvedilol may be further increased to address nonhepatic indications.

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 d until treatment goal	Without ascites: 320 mg/day; with ascites: 160 mg/day	HR of 55–60 bpm if tolerated; SBP should be maintained \geq 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 d	12.5 mg/day (higher doses could be considered for nonhepatic indications)	No HR goal; SBP should be maintained \geq 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 mo	Compensated cirrhosis with CSPH (clinical or HVPG)	Hepatic decompensation	160	Spain	NCT02643212 (CIRROXABAN)	Unknown
Anti-inflammatory	Rivaroxaban	1	12 hours	CTP A/B cirrhosis	Pharmacological	24	Switzerland	NCT04874428	Recruiting
	Belapectin	2/3	18 mo	NASH cirrhosis	New varices	1,010	United States	NCT04365868 (NAVIGATE)	Recruiting
Microbiome	Rifaximin	3	60 d	Compensated cirrhosis with CSPH (HVPG)	Change in HVPG	60	Italy	NCT02508623 (ERASE)	Unknown
Statin	Atorvastatin	4	18 mo	Compensated cirrhosis with CSPH (HVPG)	Death, LT, hospitalizations	162	Denmark	NCT04072601 (STATLiver)	Recruiting (16)
	Rosuvastatin	2/3	2 mo	Carvedilol-treated CSPH, incomplete response	Change in HVPG	80	Brazil	NCT03720067	Recruiting
Unknown	Simvastatin	3	24 mo	Compensated cirrhosis with CSPH (clinical)	Hepatic decompensation or HCC	500	United States ^a	NCT03654053 (SACRED)	Recruiting (14)
	Simvastatin ± rifaximin	3	12 mo	Decompensated cirrhosis	Incidence of ACLF	240	Europe	NCT03780673 (LiverHOPE)	Recruiting (15)
Vasodilator	BI 685509	2	24 wk	Compensated cirrhosis with CSPH (HVPG)	Change in HVPG	150	TBD	NCT05161481	Not yet recruiting
Unknown	Berberine	3	12 mo	HBV cirrhosis with VNT on carvedilol	Progression of varices	288	China	NCT04543643	Not yet recruiting

^aA 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.

DIAGNOSIS AND MONITORING

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.^[42,43] 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).^[42,43] HVPG provides valuable prognostic information in compensated and decompensated cirrhosis at baseline,^[42–45] in response to vasoactive drug therapy (such as beta-blockers),^[45–48] after elimination of the cause of cirrhosis,^[14,43,49,50] prior to resection operation for HCC,^[51] and prior to any major operation in patients with cirrhosis.^[52]

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).^[43] In such cases, endoscopic screening for complications of PH is recommended. Although HVPG measurement may also be inaccurate in some patients with NASH^[53]; HVPG values, changes in HVPG, and CSPH do retain prognostic significance among patients with NASH.^[54,55]

Although measurement of HVPG has become the gold standard to assess the presence and quantify the degree of PH,^[42] it is moderately invasive and carries small risks of injury related to access of the jugular vein, induction of arrhythmias, and exposure to radiation.^[56] Interpretation of HVPG also requires specific expertise.

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BOX 2 ABCs of HVPG measurement

1. Consider the planned approach:

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

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.

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^[57] 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).^[3,58] 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.^[23,59] For patients with chronic viral hepatitis, alcohol-associated liver disease, and lean NAFLD (body mass index <30 kg/m²), 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%.^[23]

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).^[22,23,59] CSPH can be presumed in the presence of (1) LSM > 25 kPa, (2) LSM between 20 and 25 kPa and platelets < 150 K/mm³, or (3) LSM between 15 and 20 kPa and a platelet count < 110 K/mm³. CSPH can be excluded in patients with LSM < 15 kPa plus platelets > 150 k/mm³. These cutoff values are highly specific, but there remains room for refinement because many patients remain unclassified (“gray zone”). Liver

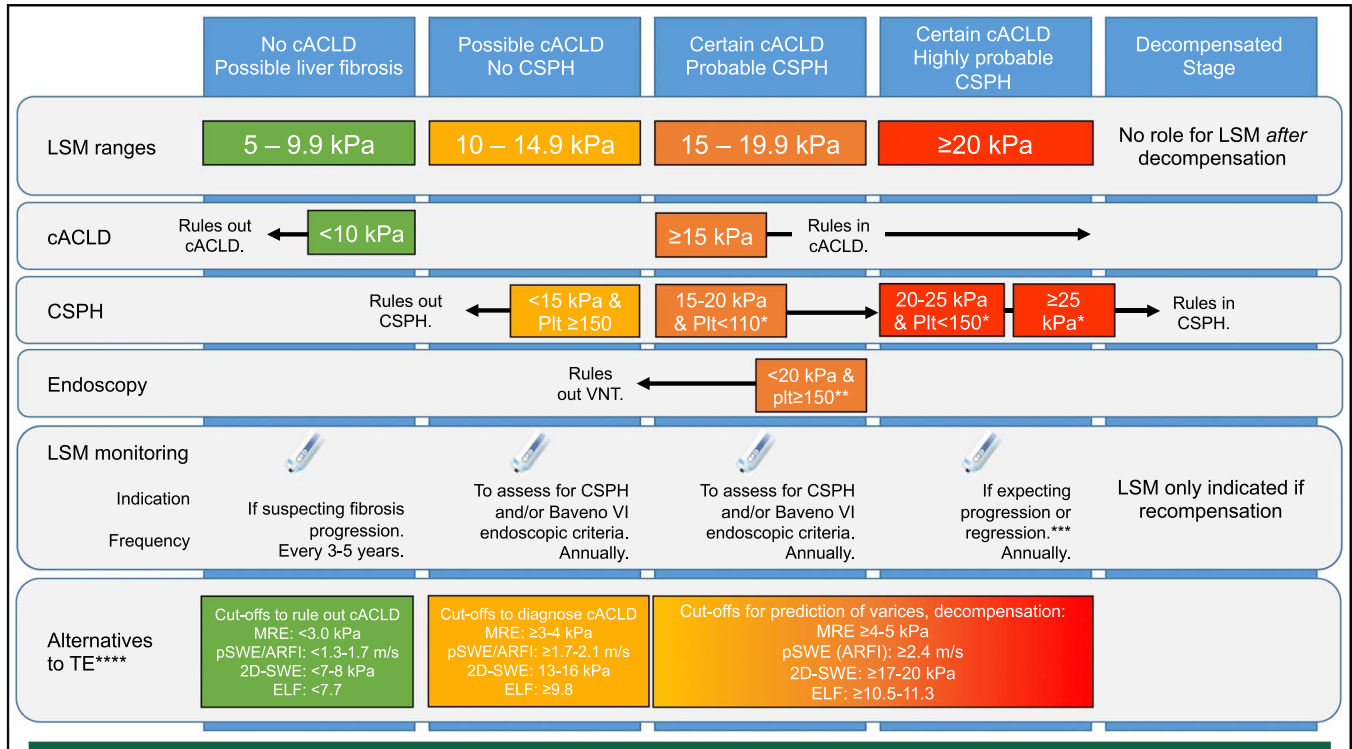


FIGURE 3 The use of noninvasive tests to stage and managed advanced chronic liver disease. Schema for using liver stiffness measurement (LSM) by transient elastography to stage advanced chronic liver disease (ACLD), identify clinically significant portal hypertension (CSPH), the stage-specific role of 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/m²). 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.

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%.^[59,60]

When HVPG values exceed 10 mm Hg, spleen stiffness measurements (SSM) by TE show a stronger correlation with HVPG than LSM.^[61] 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/mm³).^[58,62,63] Spleen length has been suggested as a proxy for spleen stiffness because the two exhibit a strong linear correlation.^[64] 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.^[65–68] 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.^[67,68] Fourteen studies have evaluated MRE for prediction of complications related to PH, but only two compared MRE with the gold-standard HVPG.^[68–71] 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.^[57] 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.^[72]

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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.^[23] Promising, but small and nonexternally validated, studies have reported good correlation of contrast-enhanced ultrasound-derived,^[73] MRI,^[74] and serum biomarkers^[75–78] 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.^[72] In the absence of LSM or spleen stiffness, platelet count has only modest predictive value for identifying CSPH^[60] and no data-supported recommendation can be made regarding the use of platelet counts in isolation to guide endoscopic surveillance or NSBB initiation.

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^[21]; (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 $\geq 20\%$ 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.

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.^[69]

Guidance statements:

3. Hepatic Venous Pressure Gradient (HVPG) measurement is the gold-standard method to assess portal pressure in patients with cirrhosis.
4. Clinically significant portal hypertension (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/mm³, or LSM 15–19.9 kPa with platelet count < 110 K/mm³.
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.

STAGE-SPECIFIC MANAGEMENT OF PH

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/mm³, 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/mm³ 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.

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 one prospective trial and a systematic meta-analysis^[4,109] 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.^[110] 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.^[97,111–113] 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.^[114] 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 C 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.^[115]

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. 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.

15. Where TE is not available to diagnose CSPH, when empiric NSBB are contraindicated or not considered due to 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).
16. Where TE is not available, screening endoscopy is not necessary in patients on non-selective beta-blocker therapy; the need for screening endoscopy can be also obviated in some patients on a selective beta-blocker by switching therapy to a non-selective beta-blocker after discussion with the prescribing clinician.

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

Patients with compensated cirrhosis who have contraindication for beta-blockers (see Box 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^[33] and retrospective studies suggest that statins reduce the incidence of decompensation,^[116,117] 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/mm³.^[118]

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.^[119–124] 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.^[125] 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.^[126] 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.^[127] 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.

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.^[128] 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.^[129] 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)^[130] and a retrospective study (HR, 0.61; 95% CI, 0.46–0.81).^[131] 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

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

Peripheral arterial disease

Chronic obstructive pulmonary disease

Pulmonary artery hypertension (controversial)

Insulin-dependent diabetes mellitus (interferes with symptoms of hypoglycemia)

Raynaud syndrome

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 vs. 4.2 y).^[132] This effect could be mediated by a decrease in the incidence of further decompensation among patients who receive NSBB.^[15,133–135]

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.^[136] 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.^[137–141] However, low systolic blood pressure (<90 mm Hg) may attenuate the survival advantage associated with NSBB use^[142,143] possibly by reducing renal perfusion pressure increasing the risk of hepatorenal syndrome—acute kidney injury.^[144] 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.^[143,145]

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.

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.^[146] 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).^[17,45,147–149] 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^[159,160] as well as antimicrobial prophylaxis should be initiated immediately on presentation and maintained for 2–5 days.^[1,159,160] 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.^[161–164] Because aspiration pneumonia is the most common infection to develop in patients admitted for variceal bleeding,^[165] 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.^[166,167] 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.^[166,168,169] 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.^[170,171] 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.^[172] Intravenous erythromycin 125–250 mg given 30–120 minutes before endoscopy has been shown to facilitate visualization and therapy.^[173,174] 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.^[175–177] 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.^[178] Many centers administer prophylactic lactulose or rifaximin to decrease the risk of HE after TIPS based on data from RCTs.^[179,180]

For specific patients who are high risk and have AVH, “early” or preemptive TIPS improves both bleeding control as well as survival in most^[50,181–183] but not all studies.^[184] 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,^[185] 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,^[186,187] but early TIPS is

still associated with lower mortality than standard therapy.^[187] 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.^[178]

Once hemostasis, hemodynamic stability, and normal mentation have been restored, oral nutrition must be started immediately to avoid malnutrition.^[188] Proton pump inhibitors should be discontinued in the absence of absolute indications because of increased risk of infection and encephalopathy.^[189–191] 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.

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 y without prophylaxis).^[127] 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.^[192] In patients who underwent preemptive TIPS, no further measures are required. Those without preemptive TIPS should receive secondary prophylaxis

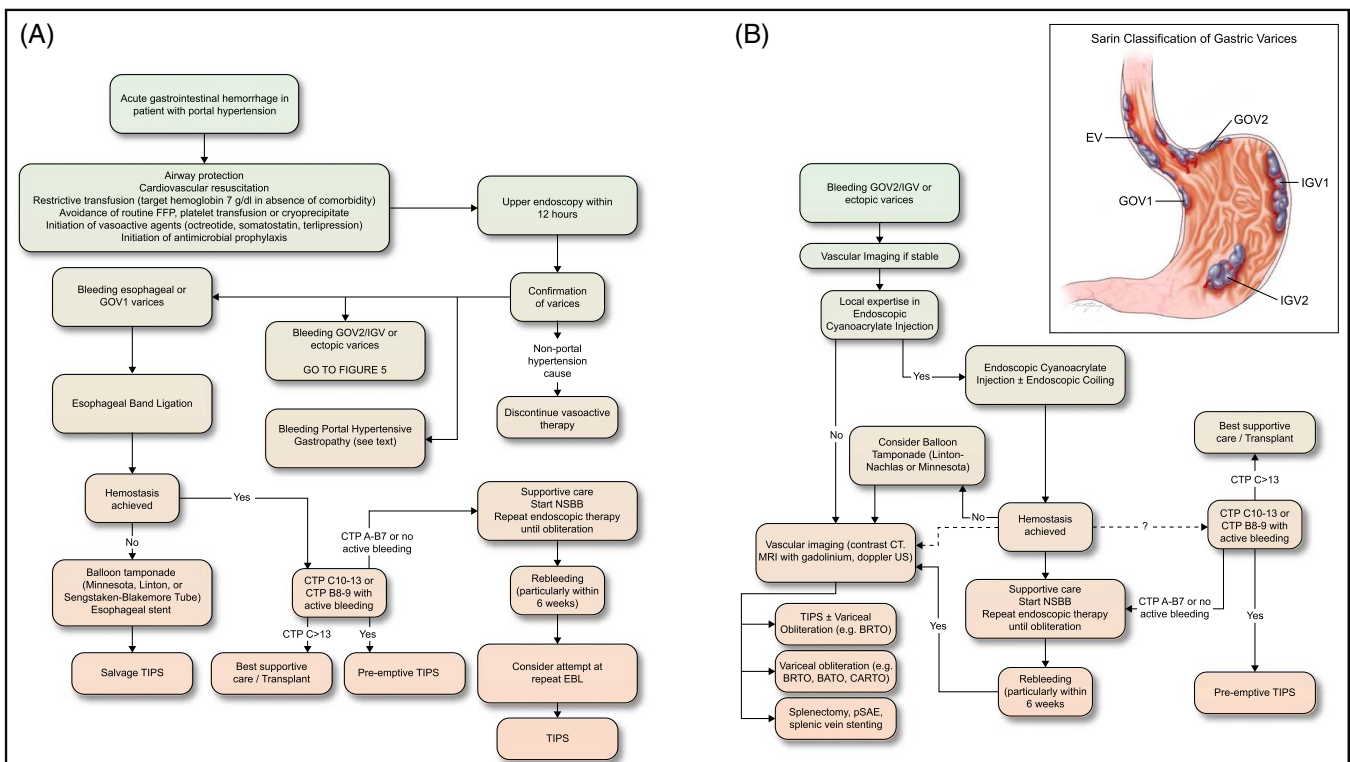


FIGURE 4 Management of acute variceal bleeding. Initial management of a patient with upper gastrointestinal bleeding that could be variceal in origin includes routine cardiopulmonary resuscitation, a conservative strategy for red cell transfusion, avoidance of routine fresh frozen plasma (FFP) and cryoprecipitate, 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.

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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 ^[151–153]	2–5 d
Somatostatin	Initial i.v. bolus of 250 mcg and continue infusion at a rate of 250–500 mcg/hour ^[154,155]	2–5 d
Terlipressin ^a	Initial 24–48 hours: 2 mg i.v. every 4–6 hours and then 1 mg i.v. every 4–6 hours ^[154,156–158]	2–5 d

^aNot approved for this indication in North America.

References: Garcia-Tsao et al. *Hepatology*. January 2017^[1]; Seo et al. *Hepatology*. September 2014.^[159]

with NSBBs and endoscopic band ligation.^[193–195] 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.^[196] Propranolol, nadolol, and carvedilol may be used for secondary prophylaxis^[29]; carvedilol has greater effects on HVPg reduction but a higher potential to cause systemic hypotension.^[197] 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.^[33] These findings, although supported by experimental data,^[198] 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^[199] for secondary prophylaxis. In such patients, one may consider adding isosorbide mononitrate,^[200] switching the NSBB to carvedilol given its greater portal pressure-reducing effect,^[197] 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.^[33,34] 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.^[38]

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.^[201,202] 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.^[203] 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.^[204]

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).

GASTRIC AND ECTOPIC VARICES

Gastric varices (GV) are commonly classified according to the Sarin classification.^[205] 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.^[205–207]

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.^[1,43,205–211] Therefore, when GV are identified, contrast-enhanced cross-sectional imaging should be performed to rule out vascular thrombosis.^[211] 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.^[210] The incidence of bleeding from cardiofundal varices is reported around 16% and 45% at 3 years.^[206,207] 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.^[1,128,212–214]

Rectal, stomal, and other ectopic varices may be identified among patients with cirrhosis and CSPH.^[215,216] 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.^[216] 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.

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^[207,217,218] (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.^[207] Performance of endovascular procedures is feasible to prevent initial hemorrhage in cardiofundal varices and has been reported effective in case series^[217,218]; however, because of the overall paucity of data and relatively high incidence of portal hypertensive complications after BRTO,^[219] 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.

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.^[219] 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^[220–223] with success rates as high as 87%–100%, mostly in small series (Supplemental Table 3, <http://links.lww.com/HEP/I69>). EVL is a therapeutic option with low/moderate rates of bleeding control (45%–93%)^[221,222]; however, rebleeding rates are higher with EVL compared with glue.^[224] 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.^[219] 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.^[223] However, BRTO and similar oblitative therapies can be associated with an increased incidence of ascites and bleeding from esophageal varices,^[219] although in others, oblitative therapy will improve liver function and reduce encephalopathy by redirecting portal flow toward the liver. The selection between TIPS or oblitative therapy should be based on patient characteristics and local expertise.^[219] 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.^[225–227] Anatomic considerations may also guide the choice of TIPS versus retrograde transvenous obliteration.^[219]

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^[228] 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,^[181] even in the setting of acute-on-chronic liver failure^[43]; it should be noted, however, that the initial trials of preemptive TIPS only included patients with esophageal varices^[181] and the specific role of preemptive TIPS in gastric and ectopic varices has only been 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,^[210] TIPS placement for gastric or ectopic

varices should be accompanied by simultaneous collateral obliteration or embolization.^[219,229] See a suggested management algorithm (Figure 4) for bleeding GV management; please refer to Abraldes et al.^[219] 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%.^[230–238] 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^[30]; 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^[219] and per recent AASLD guidance.^[219] 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 (Supplemental Table 2, <http://links.lww.com/HEP/I69>).^[221,234,235,238–243] 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.^[205] 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.^[234] A meta-analysis of observational studies suggests that BRTO is associated with lower rebleeding rates than TIPS at least in limited follow-up.^[244] Importantly, patients who underwent transvenous obliteration had significantly less encephalopathy than those with TIPS creation.^[244,245] 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.^[244,246,247] TIPS creation is associated with comparable or lower rebleeding rates than ECI but with higher rates of HE and similar survival outcomes.^[236,248] Concurrent variceal obliteration at the time of TIPS creation further reduces the risk of rebleeding as well as decreasing the risk of HE.^[229,236,244,245,246,249] 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,^[250] and splenic artery embolization^[251] 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.^[216,252–254] 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.^[255–261]

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.

ADDITIONAL TOPIC AREAS FOR GUIDANCE

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.^[262,263] 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^[264,265] (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 ectasia (GAVE) confers higher risk of hemorrhage. The prevalence of PHG among patients with compensated cirrhosis ranges from 49% to 80%,^[266–268] with lower prevalence in patients without varices (11%)^[269] or small varices (35%)^[269] relative to those with medium or large varices (80%–97%).^[268] The development of PHG usually requires the presence of CSPH.^[270,271] 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^[272]; the presence of varices and/or CTP class B/C cirrhosis are the strongest predictors of progression.^[266,268,269] Additionally, worsening of PHG features can be observed transiently after sclerotherapy or ligation of esophageal varices,^[273,274] correlating with poorer clinical outcomes.^[266]

The primary sequelae of PHG are acute and chronic hemorrhage. Acute bleeding from PHG is uncommon, occurring in 2.5%–5%^[266,268,269] 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.^[275,276] Acute administration of NSBBs reduces gastric hyperemia^[277,278] and may also attenuate bleeding in acute PHG hemorrhage.^[279] Most prospective studies suggest a potential prophylactic role for reduction of first or recurrent acute bleeding from PHG with NSBBs^[274,279–282] after exclusion of *Helicobacter pylori* as an alternative cause of mucosal granularity.^[283]

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.^[269,284] An RCT showed a clear benefit from propranolol in preventing recurrent bleeding from PHG^[282]. Recent nonrandomized data suggest that argon plasma coagulation may also attenuate chronic blood loss with chronic PHG bleeding.^[285–287] A small cases series documented some response to PHG versus GAVE-related acute bleeding with hemostatic spray.^[288] To be expected, case series of portocaval shunts^[289] and TIPS^[290] 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.^[291,292] 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.

Varices in HCC

Gastrointestinal bleeding is a known complication of anti-vascular endothelial growth factor therapies, including bevacizumab^[293] and tyrosine kinase inhibitors.^[294] Variceal hemorrhage is an infrequent complication^[295] but in most (but not all) series appears

to be increased in the presence of portal vein thrombosis.^[295–297] 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,^[298,299] recent data suggest a poor correlation between endoscopic findings and variceal bleeding and no benefit of EBL over NSBB prophylaxis.^[295] 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.^[300]

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.

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^[301]; 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.^[301] 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^[302] and TIPS^[303] for secondary prophylaxis or to control refractory variceal hemorrhage in pregnancy. Weak evidence suggests that carvedilol results in lesser fetal growth retardation in pregnancy

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.

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relative to propranolol when used for cardiac indications.^[304]

Guidance statements:

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.

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.^[305–307] 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.

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 non-visceral operation identified a reduction of acute-on-chronic liver failure and death within 90 days of operation.^[308] 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).

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.

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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Jamie Bosch receives lecture fees from Gore and consults for ICO. Maja Thiele advises Boehringer, GE Healthcare, and GSK. Brett E. Fortune consults for W.L. Gores and Associates. Douglas A. Simonetto consults for Mallinckrodt and BioVie. The remaining authors have nothing to report.

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REFERENCES

1. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 Practice Guidance by the American

Association for the Study of Liver Diseases. *Hepatology*. 2017; 65:310–35.

2. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Practice Guidelines Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007;46:922–38.
3. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, on behalf of the Baveno VII Faculty. Baveno VII - renewing consensus in portal hypertension. *J Hepatol*. 2022;76:959–74.
4. Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2019;393:1597–608.
5. Biggins SW, Angeli P, Garcia-Tsao G, Gines P, Ling SC, Nadim MK, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74:1014–48.
6. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;73:366–413.
7. Lee EW, Eghtesad B, Garcia-Tsao G, Haskal ZJ, Hernandez-Gea V, Jalaeian H, et al. AASLD Practice Guidance on the use of TIPS, variceal embolization, and retrograde transvenous obliteration in the management of variceal hemorrhage. *Hepatology*. 2023. doi: 10.1097/HEP.0000000000000530. Epub ahead of print.
8. Luca A, Cirera I, García-Pagán JC, Feu F, Pizcueta P, Bosch J, et al. Hemodynamic effects of acute changes in intra-abdominal pressure in patients with cirrhosis. *Gastroenterology*. 1993;104: 222–7.
9. Abraldes JG, Trebicka J, Chalasani N, D'Amico G, Rockey DC, Shah VH, et al. Prioritization of therapeutic targets and trial design in cirrhotic portal hypertension. *Hepatology*. 2019;69: 1287–99.
10. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: A 25-year inception cohort study of 494 patients. *Aliment Pharmacol Ther*. 2014;39:1180–93.
11. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. *J Hepatol*. 2006;44:217–31.
12. Viallet A, Marleau D, Huet M, Martin F, Farley A, Villeneuve JP, et al. Hemodynamic evaluation of patients with intrahepatic portal hypertension. Relationship between bleeding varices and the portohepatic gradient. *Gastroenterology*. 1975;69: 1297–300.
13. Joly JG, Marleau D, Legare A, Lavoie P, Bernier J, Viallet A. Bleeding from esophageal varices in cirrhosis of the liver. Hemodynamic and radiological criteria for the selection of potential bleeders through hepatic and umbilicoportal catheterization studies. *Can Med Assoc J*. 1971;104:576–80.
14. Casado M, Bosch J, García-Pagán JC, Bru C, Bañares R, Bandi JC, et al. Clinical events after transjugular intrahepatic portosystemic shunt: Correlation with hemodynamic findings. *Gastroenterology*. 1998;114:1296–303.
15. Turco L, Villanueva C, La Mura V, García-Pagán JC, Reiberger T, Genescà J, et al. Lowering portal pressure improves outcomes of patients with cirrhosis, with or without ascites: A meta-analysis. *Clin Gastroenterol Hepatol*. 2020; 18:313–27.e6.
16. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts

- clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*. 2007;133:481–8.
17. Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. *Gastroenterology*. 2014;146:412–9.e3.
 18. Fernandez M, Trépo E, Degré D, Gustot T, Verset L, Demetter P, et al. Transient elastography using Fibroscan is the most reliable noninvasive method for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease. *Eur J Gastroenterol Hepatol*. 2015;27:1074–9.
 19. Papatheodoridi M, Hiriart JB, Lupsor-Platon M, Bronte F, Boursier J, Elshaarawy O, et al. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. *J Hepatol*. 2021;74:1109–16.
 20. Shili-Masmoudi S, Wong GL, Hiriart JB, Liu K, Chermak F, Shu SS, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int*. 2020;40:581–9.
 21. Vergniol J, Foucher J, Terreboune E, Bernard PH, le Bail B, Merrouche W, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology*. 2011;140:1970–9.e3.
 22. Podrug K, Trkulja V, Zelenika M, Bokun T, Madir A, Kanizaj TF, et al. Validation of the new diagnostic criteria for clinically significant portal hypertension by platelets and elastography. *Dig Dis Sci*. 2022;67:3327–32.
 23. Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, et al. Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. *Am J Gastroenterol*. 2021;116:723–32.
 24. Semmler G, Lens S, Meyer EL, Baiges A, Alvarado-Tapias E, Llop E, et al. Non-invasive tests for clinically significant portal hypertension after HCV cure. *J Hepatol*. 2022;77:1573–85.
 25. Lens S, Baiges A, Alvarado-Tapias E, Llop E, Martinez J, Fortea JI, et al. Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. *J Hepatol*. 2020;73:1415–24.
 26. Gupta TK, Toruner M, Groszmann RJ. Intrahepatic modulation of portal pressure and its role in portal hypertension. Role of nitric oxide. *Digestion*. 1998;59:413–5.
 27. Sinagra E, Perricone G, D'Amico M, Tinè F, D'Amico G. Systematic review with meta-analysis: The haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. *Aliment Pharmacol Ther*. 2014;39:557–68.
 28. Rasool MF, Khalil F, Lâer S. Optimizing the clinical use of carvedilol in liver cirrhosis using a physiologically based pharmacokinetic modeling approach. *Eur J Drug Metab Pharmacokinet*. 2017;42:383–96.
 29. Malandris K, Paschos P, Katsoula A, Manolopoulos A, Andreadis P, Sarigianni M, et al. Carvedilol for prevention of variceal bleeding: A systematic review and meta-analysis. *Ann Gastroenterol*. 2019;32:287–97.
 30. Zacharias AP, Jeyaraj R, Hobolth L, Bendtsen F, Gluud LL, Morgan MY. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. *Cochrane Database Syst Rev*. 2018;10:CD011510.
 31. Kalambokis GN, Christaki M, Tsiakas I, Despotis G, Fillipas-Ntekouan S, Fotopoulos A, et al. Conversion of propranolol to carvedilol improves renal perfusion and outcome in patients with cirrhosis and ascites. *J Clin Gastroenterol*. 2021;55:721–9.
 32. Serper M, Kaplan DE, Taddei TH, Tapper EB, Cohen JB, Mahmud N. Nonselective beta blockers, hepatic decompensation, and mortality in cirrhosis: A national cohort study. *Hepatology*. 2023;77:489–500.
 33. Abralde JG, Albillos A, Bañares R, Turnes J, González R, García-Pagán JC, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: A randomized controlled trial. *Gastroenterology*. 2009;136:1651–8.
 34. Abralde JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J, et al. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. *Gastroenterology*. 2016;150:1160–70.e3.
 35. Pollo-Flores P, Soldan M, Santos UC, Kunz DG, Mattos DE, da Silva AC, et al. Three months of simvastatin therapy vs. placebo for severe portal hypertension in cirrhosis: A randomized controlled trial. *Dig Liver Dis*. 2015;47:957–63.
 36. Vijayaraghavan R, Jindal A, Arora V, Choudhary A, Kumar G, Sarin SK. Hemodynamic effects of adding simvastatin to carvedilol for primary prophylaxis of variceal bleeding: A randomized controlled trial. *Am J Gastroenterol*. 2020;115:729–37.
 37. Facciorusso A, Abd El Aziz MA, Singh S, Pusceddu S, Milione M, Giacomelli L, et al. Statin use decreases the incidence of hepatocellular carcinoma: An updated meta-analysis. *Cancers (Basel)*. 2020;12:874.
 38. Pose E, Napoleone L, Amin A, Campion D, Jimenez C, Piano S, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2020;5:31–41.
 39. Sung S, Al-Karaghoul M, Kalainy S, Cabrera Garcia L, Abralde JG. A systematic review on pharmacokinetics, cardiovascular outcomes and safety profiles of statins in cirrhosis. *BMC Gastroenterol*. 2021;21:120.
 40. Kaplan DE, Mehta R, Garcia-Tsao G, Albrecht J, Aytaman A, Baffy G, et al. SACRED: effect of simvastatin on hepatic decompensation and death in subjects with high-risk compensated cirrhosis: Statins and Cirrhosis: Reducing Events of Decompensation. *Contemp Clin Trials*. 2021;104:106367.
 41. Kimer N, Grønbaek H, Fred RG, Hansen T, Deshmukh AS, Mann M, et al. Atorvastatin for prevention of disease progression and hospitalisation in liver cirrhosis: Protocol for a randomised, double-blind, placebo-controlled trial. *BMJ Open*. 2020;10:e035284.
 42. Bosch J, Abralde JG, Berzigotti A, García-Pagán JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol*. 2009;6:573–82.
 43. La Mura V, Reverter JC, Flores-Arroyo A, Raffa S, Reverter E, Seijo S, et al. Von Willebrand factor levels predict clinical outcome in patients with cirrhosis and portal hypertension. *Gut*. 2011;60:1133–8.
 44. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med*. 2010;362:823–32.
 45. Moitinho E, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology*. 1999;117:626–31.
 46. La Mura V, Abralde JG, Raffa S, Retto O, Berzigotti A, García-Pagán JC, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. *J Hepatol*. 2009;51:279–87.
 47. Villanueva C, Aracil C, Colomo A, Hernández-Gea V, López-Balaguer JM, Alvarez-Urturi C, et al. Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. *Gastroenterology*. 2009;137:119–28.
 48. La Mura V, Garcia-Guix M, Berzigotti A, Abralde JG, García-Pagán JC, Villanueva C, et al. A prognostic strategy based on stage of cirrhosis and HVPG to improve risk stratification after variceal bleeding. *Hepatology*. 2020;72:1353–65.
 49. Bosch J. Small diameter shunts should lead to safe expansion of the use of TIPS. *J Hepatol*. 2021;74:230–4.

50. Nicoară-Farcău O, Han G, Rudler M, Angrisani D, Monescillo A, Torres F, et al. Effects of early placement of transjugular portosystemic shunts in patients with high-risk acute variceal bleeding: A meta-analysis of individual patient data. *Gastroenterology*. 2021;160:193–205.e10.
51. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: A systematic review and meta-analysis. *Hepatology*. 2015;61:526–36.
52. Reverter E, Cirera I, Albillos A, Debernardi-Venon W, Abraldes JG, Llop E, et al. The prognostic role of hepatic venous pressure gradient in cirrhotic patients undergoing elective extrahepatic surgery. *J Hepatol*. 2019;71:942–50.
53. Loomba R, Huang DQ, Sanyal AJ, Anstee QM, Trauner M, Lawitz EJ, et al. Liver stiffness thresholds to predict disease progression and clinical outcomes in bridging fibrosis and cirrhosis. *Gut*. 2023;72:581–9.
54. Sanyal AJ, Anstee QM, Trauner M, Lawitz EJ, Abdelmalek MF, Ding D, et al. Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. *Hepatology*. 2022;75:1235–46.
55. Harrison SA, Abdelmalek MF, Caldwell S, Shiffman ML, Diehl AM, Ghalib R, et al. Simtuzumab is ineffective for patients with bridging fibrosis or compensated cirrhosis caused by non-alcoholic steatohepatitis. *Gastroenterology*. 2018;155:1140–53.
56. Hari A, Nair HK, De Gottardi A, Baumgartner I, Dufour JF, Berzigotti A. Diagnostic hepatic haemodynamic techniques: Safety and radiation exposure. *Liver Int*. 2017;37:148–54.
57. Hai Y, Chong W, Eisenbrey JR, Forsberg F. Network meta-analysis: Noninvasive imaging modalities for identifying clinically significant portal hypertension. *Dig Dis Sci*. 2022;67:3313–26.
58. European Association for the Study of the Liver, Clinical Practice Guideline Panel. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. *J Hepatol*. 2021;75:659–89.
59. Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The “Anticipate” study. *Hepatology*. 2016;64:2173–84.
60. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology*. 2013;144:102–11.e1.
61. Colecchia A, Montrone L, Scaiola E, Bacchi-Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology*. 2012;143:646–54.
62. Fernandes FF, Filho ECC, Guimarães RA, Silva LM, Terra C, Pereira G, et al. Baveno’s VI non-invasive approach for primary prophylaxis of variceal bleeding: Can spleen stiffness help? *Hepatology*. 2015;62(S1):251A–4A.
63. Colecchia A, Ravaoli F, Marasco G, Colli A, Dajti E, Di Biase AR, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J Hepatol*. 2018;69:308–17.
64. Elshaarawy O, Mueller J, Guha IN, Chalmers J, Harris R, Krag A, et al. Spleen stiffness to liver stiffness ratio significantly differs between ALD and HCV and predicts disease-specific complications. *JHEP Rep*. 2019;1:99–106.
65. Singh S, Venkatesh SK, Wang Z, Miller FH, Motosugi U, Low RN, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: A systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol*. 2015;13:440–51.e6.
66. Natarajan Y, Loomba R. Magnetic resonance elastography for the clinical risk assessment of fibrosis, cirrhosis, and portal hypertension in patients with NAFLD. *J Clin Exp Hepatol*. 2022;12:174–9.
67. Selvaraj EA, Mózes FE, Jayaswal ANA, Zafarmand MH, Vali Y, Lee JA, et al. Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: A systematic review and meta-analysis. *J Hepatol*. 2021;75:770–85.
68. Higuchi M, Tamaki N, Kurosaki M, Inada K, Kirino S, Yamashita K, et al. Longitudinal association of magnetic resonance elastography-associated liver stiffness with complications and mortality. *Aliment Pharmacol Ther*. 2022;55:292–301.
69. Danielsen KV, Hove JD, Nabilou P, Yin M, Chen J, Zhao M, et al. Using MR elastography to assess portal hypertension and response to beta-blockers in patients with cirrhosis. *Liver Int*. 2021;41:2149–58.
70. Singh R, Wilson MP, Katlariwala P, Murad MH, McInnes MDF, Low G. Accuracy of liver and spleen stiffness on magnetic resonance elastography for detecting portal hypertension: A systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. 2021;32:237–45.
71. Ronot M, Lambert S, Elkrief L, Doblaz S, Rautou PE, Castera L, et al. Assessment of portal hypertension and high-risk oesophageal varices with liver and spleen three-dimensional multifrequency MR elastography in liver cirrhosis. *Eur Radiol*. 2014;24:1394–402.
72. Sterling RK, Asrani SK, Levine D, Duarte-Rojo A, Patel K, Fiel MI, et al. AASLD Practice Guideline: Non-Invasive Liver Disease Assessments (NILDA) of Portal Hypertension. *Hepatology*. 2023.
73. Gupta I, Eisenbrey JR, Machado P, Stanczak M, Wessner CE, Shaw CM, et al. Diagnosing portal hypertension with non-invasive subharmonic pressure estimates from a US contrast agent. *Radiology*. 2021;298:104–11.
74. Hectors SJ, Bane O, Stocker D, Carbonell G, Lewis S, Kennedy P, et al. Splenic T_{1ρ} as a noninvasive biomarker for portal hypertension. *J Magn Reson Imaging*. 2020;52:787–94.
75. Osborn J, Mourya R, Thanekar U, Su W, Fei L, Shivakumar P, et al. Serum proteomics uncovers biomarkers of clinical portal hypertension in children with biliary atresia. *Hepatol Commun*. 2022;6:995–1004.
76. Wu PS, Hsieh YC, Lee KC, Huang YH, Hou MC, Lin HC. Mac-2 binding protein glycosylation isomer is a potential biomarker to predict portal hypertension and bacterial infection in cirrhotic patients. *PLoS One*. 2021;16:e0258589.
77. Sturm L, Bettinger D, Roth L, Zoldan K, Stolz L, Gahm C, et al. Plasma cyclic guanosine monophosphate is a promising biomarker of clinically significant portal hypertension in patients with liver cirrhosis. *Front Med (Lausanne)*. 2021;8:803119.
78. Zou Z, Yan X, Li C, Li X, Ma X, Zhang C, et al. Von Willebrand factor as a biomarker of clinically significant portal hypertension and severe portal hypertension: A systematic review and meta-analysis. *BMJ Open*. 2019;9:e025656.
79. Vergniol J, Boursier J, Coutzac C, Bertrais S, Foucher J, Angel C, et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. *Hepatology*. 2014;60:65–76.
80. Wang JH, Chuah SK, Lu SN, Hung CH, Kuo CM, Tai WC, et al. Baseline and serial liver stiffness measurement in prediction of portal hypertension progression for patients with compensated cirrhosis. *Liver Int*. 2014;34:1340–8.
81. Kamarajah SK, Chan WK, Nik Mustapha NR, Mahadeva S. Repeated liver stiffness measurement compared with paired liver biopsy in patients with non-alcoholic fatty liver disease. *Hepatology Int*. 2018;12:44–55.
82. Pons M, Rodríguez-Tajes S, Esteban JI, Mariño Z, Vargas V, Lens S, et al. Non-invasive prediction of liver related events in

- HCV compensated advanced chronic liver disease patients after oral antivirals. *J Hepatol.* 2020;72:472–80.
83. Petta S, Sebastiani G, Viganò M, Ampuero J, Wong VW, Boursier J, et al. Monitoring occurrence of liver-related events and survival by transient elastography in patients with non-alcoholic fatty liver disease and compensated advanced chronic liver disease. *Clin Gastroenterol Hepatol.* 2021;19:806–15.e5.
 84. Semmler G, Binter T, Kozbial K, Schwabl P, Hametner-Schreil S, Zanetto A, et al. Noninvasive risk stratification after HCV eradication in patients with advanced chronic liver disease. *Hepatology.* 2021;73:1275–89.
 85. Nascimbeni F, Lebray P, Fedchuk L, Oliveira CP, Alvares-da-Silva MR, Varault A, et al. Significant variations in elastometry measurements made within short-term in patients with chronic liver diseases. *Clin Gastroenterol Hepatol.* 2015;13:763–71.e6.
 86. Chow JC, Wong GL, Chan AW, Shu SS, Chan CK, Leung JK, et al. Repeating measurements by transient elastography in non-alcoholic fatty liver disease patients with high liver stiffness. *J Gastroenterol Hepatol.* 2019;34:241–8.
 87. Legros L, Bardou-Jacquet E, Turlin B, Michalak S, Hamonic S, Le Gruyer A, et al. Transient elastography accurately screens for compensated advanced chronic liver disease in patients with ongoing or recent alcohol withdrawal. *Clin Gastroenterol Hepatol.* 2022;20:1542–52.e6.
 88. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. *BMJ.* 2016;353:i3139.
 89. Kim HY, So YH, Kim W, Ahn DW, Jung YJ, Woo H, et al. Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices. *J Hepatol.* 2019;70:412–22.
 90. Marasco G, Dajti E, Ravaoli F, Alemanni LV, Capuano F, Gjini K, et al. Spleen stiffness measurement for assessing the response to β -blockers therapy for high-risk esophageal varices patients. *Hepatol Int.* 2020;14:850–7.
 91. Ripoll C. Hepatic venous pressure gradient and outcomes in cirrhosis. *J Clin Gastroenterol.* 2007;41(Suppl 3S):330–5.
 92. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2018;68:723–50.
 93. Simón-Talero M, Roccarina D, Martínez J, Lampichler K, Baiges A, Low G, et al. Association between portosystemic shunts and increased complications and mortality in patients with cirrhosis. *Gastroenterology.* 2018;154:1694–705.e4.
 94. de Franchis R, Baveno VI, Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63:743–52.
 95. Bertrais S, Boursier J, Ducancelle A, Oberti F, Fouchard-Hubert I, Moal V, et al. Prognostic durability of liver fibrosis tests and improvement in predictive performance for mortality by combining tests. *J Gastroenterol Hepatol.* 2017;32:1240–9.
 96. Rasmussen DN, Thiele M, Johansen S, Kjærgaard M, Lindvig KP, Israelsen M, et al. Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. *J Hepatol.* 2021;75:1017–25.
 97. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med.* 2005;353:2254–61.
 98. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study. *Lancet.* 2013;381:468–75.
 99. Parker R, Aithal GP, Becker U, Gleeson D, Masson S, Wyatt JI, et al. On behalf of the WALDO study group. Natural history of histologically proven alcohol-related liver disease: A systematic review. *J Hepatol.* 2019;71:586–93.
 100. Rockey DC, Friedman SL. Fibrosis regression after eradication of hepatitis C virus: From bench to bedside. *Gastroenterology.* 2021;160:1502–20.e1.
 101. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al for the NATIVE Study Group. A randomized, controlled trial of the Pan-PPAR agonist lanifibranor in NASH. *N Engl J Med.* 2021;385:1547–58.
 102. Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet.* 2019;394:2184–96.
 103. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al for the NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384:1113–24.
 104. Vilar-Gomez E, Calzadilla-Bertot L, Wong VW, Castellanos M, Aller-de la Fuente R, Eslam M, et al. Type 2 diabetes and metformin use associate with outcomes of patients with nonalcoholic steatohepatitis-related, Child-Pugh A cirrhosis. *Clin Gastroenterol Hepatol.* 2021;19:136–45.e6.
 105. Kaplan DE, Serper M, John BV, Tessitore KM, Lerer R, Mehta R, et al. Veterans Outcomes and Cost Associated with Liver disease Study Group. Effects of metformin exposure on survival in a large national cohort of patients with diabetes and cirrhosis. *Clin Gastroenterol Hepatol.* 2021;19:2148–60.e14.
 106. Rittig N, Aagaard NK, Villadsen GE, Sandahl TD, Jessen N, Grønbaek H, et al. Randomised clinical study: Acute effects of metformin versus placebo on portal pressure in patients with cirrhosis and portal hypertension. *Aliment Pharmacol Ther.* 2021;54:320–8.
 107. Simon TG, Duberg AS, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N Engl J Med.* 2020;382:1018–28.
 108. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology.* 1985;5:419–24.
 109. Villanueva C, Torres F, Sarin SK, Shah HA, Tripathi D, Brujats A, et al. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. *J Hepatol.* 2022;77:1014–25.
 110. Rowe IA, Villanueva C, Shearer JE, Torres F, Albillos A, Genescà J, et al for the PREDESCI trial investigators. Quantifying the benefit of non-selective beta-blockers in the prevention of hepatic decompensation: A Bayesian re-analysis of the PREDESCI trial. *Hepatology.* 2023;78:530–9.
 111. D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci.* 1986;31:468–75.
 112. Pagliaro L, D'Amico G, Pasta L. Portal hypertension in cirrhosis: Natural history. In: Bosch J, Groszmann RJ, ed. *Portal hypertension Pathophysiology and treatment.* Oxford, UK: Blackwell Scientific; 1994:72–92.
 113. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol.* 2003;38:266–72.
 114. D'Amico G, Pagliaro L. The clinical course of portal hypertension in liver cirrhosis. In: Rossi P, Ricci P, Broglia L, eds. *Portal hypertension Medical radiology.* Berlin, Germany: Springer; 2000:15–24.
 115. Tosetti G, Degasperis E, Farina E, D'Ambrosio R, Soffredini R, Borghi M, et al. Decompensation in direct-acting antiviral cured hepatitis C virus compensated patients with clinically significant

- portal hypertension: Too rare to warrant universal beta-blocker therapy. *Am J Gastroenterol.* 2021;116:1342–4.
116. Mohanty A, Tate JP, Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. *Gastroenterology.* 2016;150:430–40.e1.
 117. Kaplan DE, Serper MA, Mehta R, Fox R, John B, Aytaman A, et al. Effects of hypercholesterolemia and statin exposure on survival in a large national cohort of patients with cirrhosis. *Gastroenterology.* 2019;156:1693–706.e12.
 118. Tonon M, Balcar L, Semmler G, Calvino V, Scheiner B, Incicco S, et al. Etiological cure prevents further decompensation and mortality in cirrhotic patients with ascites as the single first decompensating event. *J Hepatol.* 2022;77(S1):S18–9.
 119. Lay CS, Tsai YT, Lee FY, Lai YL, Yu CJ, Chen CB, et al. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. *J Gastroenterol Hepatol.* 2006;21:413–9.
 120. Lo GH, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI, et al. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. *Gastrointest Endosc.* 2004;59:333–8.
 121. Schepke M, Kleber G, Nürnberg D, Willert J, Koch L, Veltke-Schlieker W, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology.* 2004;40:65–72.
 122. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol.* 2005;100:797–804.
 123. Villanueva C, Miñana J, Ortiz J, Gallego A, Soriano G, Torras X, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med.* 2001;345:647–55.
 124. Wang HM, Lo GH, Chen WC, Tsai WL, Chan HH, Cheng LC, et al. Comparison of endoscopic variceal ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first variceal bleeding in cirrhotic patients. *J Chin Med Assoc.* 2006;69:453–60.
 125. Yoshida H, Mamada Y, Taniai N, Yamamoto K, Kawano Y, Mizuguchi Y, et al. A randomized control trial of bi-monthly versus bi-weekly endoscopic variceal ligation of esophageal varices. *Am J Gastroenterol.* 2005;100:2005–9.
 126. Sheibani S, Khemichian S, Kim JJ, Hou L, Yan AW, Buxbaum J, et al. Randomized trial of 1-week versus 2-week intervals for endoscopic ligation in the treatment of patients with esophageal variceal bleeding. *Hepatology.* 2016;64:549–55.
 127. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: A meta-analytic review. *Hepatology.* 1995;22:332–54.
 128. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. *N Engl J Med.* 1988;319:983–9.
 129. Sharma M, Singh S, Desai V, Shah VH, Kamath PS, Murad MH, et al. Comparison of therapies for primary prevention of esophageal variceal bleeding: A systematic review and network meta-analysis. *Hepatology.* 2019;69:1657–75.
 130. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology.* 2009;50:825–33.
 131. Sinha R, Lockman KA, Mallawaarachchi N, Robertson M, Plevris JN, Hayes PC. Carvedilol use is associated with improved survival in patients with liver cirrhosis and ascites. *J Hepatol.* 2017;67:40–6.
 132. McDowell HR, Chuah CS, Tripathi D, Stanley AJ, Forrest EH, Hayes PC. Carvedilol is associated with improved survival in patients with cirrhosis: A long-term follow-up study. *Aliment Pharmacol Ther.* 2021;53:531–9.
 133. Senzolo M, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, et al. β -blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int.* 2009;29:1189–93.
 134. Jachs M, Hartl L, Simbrunner B, Bauer D, Paternostro R, Scheiner B, et al. Decreasing von Willebrand factor levels upon nonselective beta blocker therapy indicate a decreased risk of further decompensation, acute-on-chronic liver failure, and death. *Clin Gastroenterol Hepatol.* 2022;20:1362–73.e6.
 135. Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, et al. for the CANONIC Study Investigators of the EASL-CLIF Consortium. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol.* 2016;64:574–82.
 136. Sersté T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology.* 2010;52:1017–22.
 137. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective β blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology.* 2014;146:1680–90.e1.
 138. Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective β -blockers are associated with improved survival in patients with ascites listed for liver transplantation. *Gut.* 2015;64:1111–9.
 139. Bossen L, Krag A, Vilstrup H, Watson H, Jepsen P. Nonselective β -blockers do not affect mortality in cirrhosis patients with ascites: Post hoc analysis of three randomized controlled trials with 1198 patients. *Hepatology.* 2016;63:1968–76.
 140. Wong RJ, Robinson A, Ginzberg D, Gomes C, Liu B, Bhuket T. Assessing the safety of beta-blocker therapy in cirrhosis patients with ascites: A meta-analysis. *Liver Int.* 2019;39:1080–8.
 141. Kimer N, Feineis M, Møller S, Bendtsen F. Beta-blockers in cirrhosis and refractory ascites: A retrospective cohort study and review of the literature. *Scand J Gastroenterol.* 2015;50:129–37.
 142. Tergast TL, Kimmann M, Laser H, Gerbel S, Manns MP, Comberg M, et al. Systemic arterial blood pressure determines the therapeutic window of non-selective beta blockers in decompensated cirrhosis. *Aliment Pharmacol Ther.* 2019;50:696–706.
 143. Bhutta AQ, Garcia-Tsao G, Reddy KR, Tandon P, Wong F, O'Leary JG, et al. Beta-blockers in hospitalised patients with cirrhosis and ascites: Mortality and factors determining discontinuation and reinitiation. *Aliment Pharmacol Ther.* 2018;47:78–85.
 144. Téllez L, Ibáñez-Samaniego L, Pérez Del Villar C, Yotti R, Martínez J, Carrión L, et al. Non-selective beta-blockers impair global circulatory homeostasis and renal function in cirrhotic patients with refractory ascites. *J Hepatol.* 2020;73:1404.
 145. Njei B, McCarty TR, Garcia-Tsao G. Beta-blockers in patients with cirrhosis and ascites: type of beta-blocker matters. *Gut.* 2016;65:1393–4.
 146. Escorsell A, Bordas JM, Feu F, García-Pagán JC, Ginès A, Bosch J, et al. Endoscopic assessment of variceal volume and wall tension in cirrhotic patients: Effects of pharmacological therapy. *Gastroenterology.* 1997;113:1640–6.
 147. Abralde JG, Villanueva C, Bañares R, Aracil C, Catalina MV, García-Pagán JC, et al. for the Spanish Cooperative Group for Portal Hypertension and Variceal Bleeding. Hepatic venous pressure gradient and prognosis in patients with acute variceal

- bleeding treated with pharmacologic and endoscopic therapy. *J Hepatol*. 2008;48:229–36.
148. Fortune BE, Garcia-Tsao G, Ciarleglio M, Deng Y, Fallon MB, Sigal S, et al. Child-Turcotte-Pugh class is best at stratifying risk in variceal hemorrhage: Analysis of a US multicenter prospective study. *J Clin Gastroenterol*. 2017;51:446–53.
 149. Augustin S, Muntaner L, Altamirano JT, González A, Saperas E, Dot J, et al. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. *Clin Gastroenterol Hepatol*. 2009;7:1347–54.
 150. Sasso R, Lauzon S, Rockey DC. Cirrhotic patients on mechanical ventilation have a low rate of successful extubation and survival. *Dig Dis Sci*. 2020;65:3744–52.
 151. Hwang SJ, Lin HC, Chang CF, Lee FY, Lu CW, Hsia HC, et al. A randomized controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal bleeding. *J Hepatol*. 1992;16:320–5.
 152. Rengasamy S, Ali SM, Sistla SC, Lakshmi CP, Harichandra Kumar KT. Comparison of 2 days versus 5 days of octreotide infusion along with endoscopic therapy in preventing early rebleed from esophageal varices: A randomized clinical study. *Eur J Gastroenterol Hepatol*. 2015;27:386–92.
 153. Sung JJ, Chung SC, Yung MY, Lai CW, Lau JY, Lee YT, et al. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet*. 1995;346(8991–8992):1666–9.
 154. Feu F, Ruiz del Arbol L, Bañares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. *Variceal Bleeding Study Group. Gastroenterology*. 1996;111:1291–9.
 155. Avgerinos A, Nevens F, Raptis S, Fevery J. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: The European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. *Lancet*. 1997;350:1495–9.
 156. Abid S, Jafri W, Hamid S, Salih M, Azam Z, Mumtaz K, et al. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: A randomized double-blind placebo-controlled trial. *Am J Gastroenterol*. 2009;104:617–23.
 157. Freeman JG, Cobden I, Lishman AH, Record CO. Controlled trial of terlipressin ('Glypressin') versus vasopressin in the early treatment of oesophageal varices. *Lancet*. 1982;2:66–8.
 158. Walker S, Stiehl A, Raedsch R, Kommerell B. Terlipressin in bleeding esophageal varices: A placebo-controlled, double-blind study. *Hepatology*. 1986;6:112–5.
 159. Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. *Hepatology*. 2014;60:954–63.
 160. Wells M, Chande N, Adams P, Beaton M, Levstik M, Boyce E, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. *Aliment Pharmacol Ther*. 2012;35:1267–78.
 161. Amitrano L, Guardascione MA, Manguso F, Bennato R, Bove A, DeNucci C, et al. The effectiveness of current acute variceal bleed treatments in unselected cirrhotic patients: Refining short-term prognosis and risk factors. *Am J Gastroenterol*. 2012;107:1872–8.
 162. Bernard B, Grangé JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: A meta-analysis. *Hepatology*. 1999;29:1655–61.
 163. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. *Aliment Pharmacol Ther*. 2011;34:509–18.
 164. Fernández J, Ruiz del Arbol L, Gómez C, Durandez R, Serradilla R, Guamer C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131:1049–56; quiz 1285.
 165. Sorbi D, Gostout CJ, Peura D, Johnson D, Lanza F, Foutch PG, et al. An assessment of the management of acute bleeding varices: A multicenter prospective member-based study. *Am J Gastroenterol*. 2003;98:2424–34.
 166. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368:11–21.
 167. Odutayo A, Desborough MJ, Trivella M, Stanley AJ, Dorée C, Collins GS, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: A systematic review and meta-analysis of randomised controlled trials. *Lancet Gastroenterol Hepatol*. 2017;2:354–60.
 168. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in cirrhosis. *Gastroenterology*. 2019;157:34–43.e1.
 169. Mohanty A, Kapuria D, Canakis A, Lin H, Amat MJ, Rangel Paniz G, et al. Fresh frozen plasma transfusion in acute variceal haemorrhage: Results from a multicentre cohort study. *Liver Int*. 2021;41:1901–8.
 170. Chen PH, Chen WC, Hou MC, Liu TT, Chang CJ, et al. Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal bleeding: a cohort study. *J Hepatol*. 2012;57:1207–13.
 171. Bai Z, Wang R, Cheng G, Ma D, Ibrahim M, et al. Outcomes of early versus delayed endoscopy in cirrhotic patients with acute variceal bleeding: a systematic review with meta-analysis. *Eur J Gastro Heo*. 2021;33:e868–76.
 172. Saeed ZA, Stiegmann GV, Ramirez FC, Reveille RM, Goff JS, Hepps KS, et al. Endoscopic variceal ligation is superior to combined ligation and sclerotherapy for esophageal varices: A multicenter prospective randomized trial. *Hepatology*. 1997;25:71–4.
 173. Altraif I, Handoo FA, Aljumah A, Alalwan A, Dafalla M, Saeed AM, et al. Effect of erythromycin before endoscopy in patients presenting with variceal bleeding: A prospective, randomized, double-blind, placebo-controlled trial. *Gastrointest Endosc*. 2011;73:245–50.
 174. Rahman R, Nguyen DL, Sohail U, Almashhrawi AA, Ashraf I, Puli SR, et al. Pre-endoscopic erythromycin administration in upper gastrointestinal bleeding: An updated meta-analysis and systematic review. *Ann Gastroenterol*. 2016;29:312–7.
 175. Escorsell A, Pavel O, Cárdenas A, Morillas R, Llop E, Villanueva C, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. *Hepatology*. 2016;63:1957–67.
 176. McCarty TR, Njei B. Self-expanding metal stents for acute refractory esophageal variceal bleeding: A systematic review and meta-analysis. *Dig Endosc*. 2016;28:539–47.
 177. Rodrigues SG, Cardenas A, Escorsell A, Bosch J. Balloon tamponade and esophageal stenting for esophageal variceal bleeding in cirrhosis: A systematic review and meta-analysis. *Semin Liver Dis*. 2019;39:178–94.
 178. Maimone S, Saffioti F, Filomia R, Alibrandi A, Isgrò G, Calvaruso V, et al. Predictors of re-bleeding and mortality among patients with refractory variceal bleeding undergoing salvage transjugular intrahepatic portosystemic shunt (TIPS). *Dig Dis Sci*. 2019;64:1335–45.
 179. Seifert LL, Schindler P, Schoster M, Weller JF, Wilms C, Schmidt HH, et al. Recurrence of hepatic encephalopathy after TIPS: effective prophylaxis with combination of lactulose and rifaximin. *J Clin Med*. 2021;10:4763.
 180. Bureau C, Thabut D, Jezequel C, Archambeaud I, D'Alteroche L, Dharancy S, et al. The use of rifaximin in the prevention of overt hepatic encephalopathy after transjugular intrahepatic

- portosystemic shunt: A randomized controlled trial. *Ann Intern Med.* 2021;174:633–40.
181. García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al for the Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med.* 2010;362:2370–9.
 182. Hernández-Gea V, Procopet B, Giráldez A, Amitrano L, Villanueva C, Thabut D, et al. Preemptive-TIPS improves outcome in high-risk variceal bleeding: An observational study. *Hepatology.* 2019;69:282–93.
 183. Trebicka J, Gu W, Ibáñez-Samaniego L, Hernández-Gea V, Pitarch C, Garcia E, et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. *J Hepatol.* 2020;73:1082–91.
 184. Dunne PDJ, Sinha R, Stanley AJ, Lachlan N, Ireland H, Shams A, et al. Randomised clinical trial: Standard of care versus early-transjugular intrahepatic porto-systemic shunt (TIPSS) in patients with cirrhosis and oesophageal variceal bleeding. *Aliment Pharmacol Ther.* 2020;52:98–106.
 185. Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology.* 2004;40:793–801.
 186. Hermie L, Dhondt E, Vanlangenhove P, Hoste E, Geerts A, Defreyne L. Model for End-Stage Liver Disease score and hemodynamic instability as a predictor of poor outcome in early transjugular intrahepatic portosystemic shunt treatment for acute variceal hemorrhage. *Eur J Gastroenterol Hepatol.* 2018; 30:1441–6.
 187. Lv Y, Yang Z, Liu L, Li K, He C, Wang Z, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: A randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2019;4: 587–98.
 188. Tsai MH, Huang HC, Peng YS, Chen YC, Tian YC, Yang CW, et al. Nutrition risk assessment using the modified NUTRIC score in cirrhotic patients with acute gastroesophageal variceal bleeding: Prevalence of high nutrition risk and its independent prognostic value. *Nutrients.* 2019;11:2152.
 189. O’Leary JG, Reddy KR, Wong F, Kamath PS, Patton HM, Biggins SW, et al on behalf of the North American Consortium for the Study of End-Stage Liver Disease. Long-term use of antibiotics and proton pump inhibitors predict development of infections in patients with cirrhosis. *Clin Gastroenterol Hepatol.* 2015;13:753–9.e2.
 190. Dam G, Vilstrup H, Andersen PK, Bossen L, Watson H, Jepsen P. Effect of proton pump inhibitors on the risk and prognosis of infections in patients with cirrhosis and ascites. *Liver Int.* 2019; 39:514–21.
 191. Thomson MJ, Lok ASF, Tapper EB. Appropriate and potentially inappropriate medication use in decompensated cirrhosis. *Hepatology.* 2021;73:2429–40.
 192. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology.* 1981;80:800–9.
 193. Cheung J, Zeman M, van Zanten SV, Tandon P. Systematic review: secondary prevention with band ligation, pharmacotherapy or combination therapy after bleeding from oesophageal varices. *Aliment Pharmacol Ther.* 2009;30:577–88.
 194. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Bañares R, Albillos A. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med.* 2008;149:109–22.
 195. Puente A, Hernández-Gea V, Graupera I, Roque M, Colomo A, Poca M, et al. Drugs plus ligation to prevent rebleeding in cirrhosis: An updated systematic review. *Liver Int.* 2014;34:823–33.
 196. Albillos A, Zamora J, Martínez J, Arroyo D, Ahmad I, De-la-Peña J, et al. Stratifying risk in the prevention of recurrent variceal hemorrhage: Results of an individual patient meta-analysis. *Hepatology.* 2017;66:1219–31.
 197. Gupta V, Rawat R, Shalimar, Saraya A. Carvedilol versus propranolol effect on hepatic venous pressure gradient at 1 month in patients with index variceal bleed: RCT. *Hepatol Int.* 2017;11:181–7.
 198. Tripathi DM, Vilaseca M, Lafoz E, Garcia-Calderó H, Viegas Haute G, Fernández-Iglesias A, et al. Simvastatin prevents progression of acute on chronic liver failure in rats with cirrhosis and portal hypertension. *Gastroenterology.* 2018;155:1564–77.
 199. de Souza AR, La Mura V, Reverter E, Seijo S, Berzigotti A, Ashkenazi E, et al. Patients whose first episode of bleeding occurs while taking a β -blocker have high long-term risks of rebleeding and death. *Clin Gastroenterol Hepatol.* 2012;10: 670–6; quiz e58.
 200. Kong Y, Shi L. Comparison of the effectiveness of 11 mainstay treatments for secondary prophylaxis of variceal bleeding in patients with cirrhosis: A network meta-analysis. *Exp Ther Med.* 2020;19:3479–96.
 201. Sauerbruch T, Mengel M, Dollinger M, Zipprich A, Rössle M, Panther E, et al. Prevention of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents versus hemodynamically controlled medical therapy. *Gastroenterology.* 2015;149:660–8.e1.
 202. Holster IL, Tjwa ET, Moelker A, Wils A, Hansen BE, Vermeijden JR, et al. Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy + β -blocker for prevention of variceal rebleeding. *Hepatology.* 2016;63:581–9.
 203. Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. *Gastroenterology.* 2017; 152:157–63.
 204. Ardevol A, Alvarado-Tapias E, Garcia-Guix M, Brujats A, Gonzalez L, Hernández-Gea V, et al. Early rebleeding increases mortality of variceal bleeders on secondary prophylaxis with β -blockers and ligation. *Dig Liver Dis.* 2020;52: 1017–25.
 205. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: A long-term follow-up study in 568 portal hypertension patients. *Hepatology.* 1992;16:1343–9.
 206. Henry Z, Patel K, Patton H, Saad W. AGA clinical practice update on management of bleeding gastric varices: Expert review. *Clin Gastroenterol Hepatol.* 2021;19:1098–7.e1.
 207. Mishra SR, Sharma BC, Kumar A, Sarin SK. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: A randomized controlled trial. *J Hepatol.* 2011;54:1161–7.
 208. Watanabe K, Kimura K, Matsutani S, Ohto M, Okuda K. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology.* 1988;95:434–40.
 209. Sanyal AJ, Freedman AM, Luketic VA, Purdum PP III, Shiffman ML, DeMeo J, et al. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. *Gastroenterology.* 1997;112:889–98.
 210. Tripathi D, Therapondos G, Jackson E, Redhead DN, Hayes PC. The role of the transjugular intrahepatic portosystemic shunt (TIPSS) in the management of bleeding gastric varices: Clinical and haemodynamic correlations. *Gut.* 2002;51:270–4.
 211. Saad WE. Vascular anatomy and the morphologic and hemodynamic classifications of gastric varices and spontaneous portosystemic shunts relevant to the BRTO procedure. *Tech Vasc Interv Radiol.* 2013;16:60–100.
 212. Hashizume M, Kitano S, Yamaga H, Koyanagi N, Sugimachi K. Endoscopic classification of gastric varices. *Gastrointest Endosc.* 1990;36:276–80.

213. Kang EJ, Jeong SW, Jang JY, Cho JY, Lee SH, Kim HG, et al. Long-term result of endoscopic Histoacryl® (N-butyl-2-cyanoacrylate) injection for treatment of gastric varices. *World J Gastroenterol*. 2011;17:1494–500.
214. Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Ota K, et al. Risk factors for hemorrhage from gastric fundal varices. *Hepatology*. 1997;25:307–12.
215. Rabinovitz M, Schade RR, Dindzans VJ, Belle SH, Van Thiel DH, Gavaler JS. Colonic disease in cirrhosis. An endoscopic evaluation in 412 patients. *Gastroenterology*. 1990;99:195–9.
216. Jansson-Knodell CL, Calderon G, Weber R, Ghabril M. Small intestine varices in cirrhosis at a high-volume liver transplant center: A retrospective database study and literature review. *Am J Gastroenterol*. 2021;116:1426–36.
217. Takuma Y, Nouse K, Makino Y, Saito S, Shiratori Y. Prophylactic balloon-occluded retrograde transvenous obliteration for gastric varices in compensated cirrhosis. *Clin Gastroenterol Hepatol*. 2005;3:1245–52.
218. Shiba M, Higuchi K, Nakamura K, Itani A, Kuga T, Okazaki H, et al. Efficacy and safety of balloon-occluded endoscopic injection sclerotherapy as a prophylactic treatment for high-risk gastric fundal varices: a prospective, randomized, comparative clinical trial. *Gastrointest Endosc*. 2002;56:522–8.
219. Saad WE. Balloon-occluded retrograde transvenous obliteration of gastric varices: concept, basic techniques, and outcomes. *Semin Intervent Radiol*. 2012;29:118–28.
220. Tantau M, Crisan D, Popa D, Vesa S, Tantau A. Band ligation vs. N-Butyl-2-cyanoacrylate injection in acute gastric variceal bleeding: A prospective follow-up study. *Ann Hepatol*. 2013;13:75–83.
221. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology*. 2001;33:1060–4.
222. Tan PC, Hou MC, Lin HC, Liu TT, Lee FY, Chang FY, et al. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. *Hepatology*. 2006;43:690–7.
223. Hong CH, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. Treatment of patients with gastric variceal hemorrhage: Endoscopic N-butyl-2-cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration. *J Gastroenterol Hepatol*. 2009;24:372–8.
224. Ríos Castellanos E, Seron P, Gisbert JP, Bonfill Cosp X. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension. *Cochrane Database Syst Rev*. 2015; 12:CD010180. doi: 10.1002/14651858.CD010180.pub2.
225. Boike JR, Mazumder NR, Kolli KP, Ge J, German M, Jest N, et al. Outcomes after TIPS for ascites and variceal bleeding in a contemporary era—an ALTA Group Study. *Am J Gastroenterol*. 2021;116:2079–88.
226. Bettinger D, Sturm L, Pfaff L, Hahn F, Kloeckner R, Volkwein L, et al. Refining prediction of survival after TIPS with the novel Freiburg index of post-TIPS survival. *J Hepatol*. 2021;74:1362–72.
227. Chapin SE, Goldberg DS, Kaplan DE, Mahmud N. External validation of the FIPS score for post-TIPS mortality in a national Veterans Affairs cohort. *Dig Dis Sci*. 2022;67:4581–9.
228. Chau TN, Patch D, Chan YW, Nagral A, Dick R, Burroughs AK. “Salvage” transjugular intrahepatic portosystemic shunts: Gastric fundal compared with esophageal variceal bleeding. *Gastroenterology*. 1998;114:981–7.
229. Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: Concept and technical applications. *Tech Vasc Interv Radiol*. 2012;15:203–25.
230. Kim DJ, Darcy MD, Mani NB, Park AW, Akinwande O, Ramaswamy RS, et al. Modified balloon-occluded retrograde transvenous obliteration (BRTO) techniques for the treatment of gastric varices: Vascular plug-assisted retrograde transvenous obliteration (PARTO)/coil-assisted retrograde transvenous obliteration (CARTO)/balloon-occluded antegrade transvenous obliteration (BATO). *Cardiovasc Intervent Radiol*. 2018;41: 835–47.
231. Sabri SS, Swee W, Turba UC, Saad WE, Park AW, Al-Osaimi AM, et al. Bleeding gastric varices obliteration with balloon-occluded retrograde transvenous obliteration using sodium tetradecyl sulfate foam. *J Vasc Interv Radiol*. 2011;22:309–16; quiz 316.
232. Imai Y, Nakazawa M, Ando S, Sugawara K, Mochida S. Long-term outcome of 154 patients receiving balloon-occluded retrograde transvenous obliteration for gastric fundal varices. *J Gastroenterol Hepatol*. 2016;31:1844–50.
233. Park JK, Saab S, Kee ST, Busuttill RW, Kim HJ, Durazo F, et al. Balloon-occluded retrograde transvenous obliteration (BRTO) for treatment of gastric varices: review and meta-analysis. *Dig Dis Sci*. 2015;60:1543–53.
234. Luo X, Xiang T, Wu J, Wang X, Zhu Y, Xi X, et al. Endoscopic cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration for prevention of gastric variceal bleeding: A randomized controlled trial. *Hepatology*. 2021;74:2074–84.
235. Mishra SR, Chander Sharma B, Kumar A, Sarin SK. Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: A randomised controlled trial. *Gut*. 2010;59:729–35.
236. Lo GH, Liang HL, Chen WC, Chen MH, Lai KH, Hsu PI, et al. A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. *Endoscopy*. 2007; 39:679–85.
237. Sabri SS, Abi-Jaoudeh N, Swee W, Saad WE, Turba UC, Caldwell SH, et al. Short-term rebleeding rates for isolated gastric varices managed by transjugular intrahepatic portosystemic shunt versus balloon-occluded retrograde transvenous obliteration. *J Vasc Interv Radiol*. 2014;25:355–61.
238. Hung HH, Chang CJ, Hou MC, Liao WC, Chan CC, Huang HC, et al. Efficacy of non-selective β -blockers as adjunct to endoscopic prophylactic treatment for gastric variceal bleeding: A randomized controlled trial. *J Hepatol*. 2012;56:1025–32.
239. Baig M, Ramchandani M, Puli SR. Safety and efficacy of endoscopic ultrasound-guided combination therapy for treatment of gastric varices: A systematic review and meta-analysis. *Clin J Gastroenterol*. 2022;15:310–9.
240. Lee YT, Chan FK, Ng EK, Leung VK, Law KB, Yung MY, et al. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc*. 2000;52:168–74.
241. Binmoeller KF, Weilert F, Shah JN, Kim J. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). *Gastrointest Endosc*. 2011;74:1019–25.
242. Bhat YM, Weilert F, Fredrick RT, Kane SD, Shah JN, Hamerski CM, et al. EUS-guided treatment of gastric fundal varices with combined injection of coils and cyanoacrylate glue: A large U.S. experience over 6 years (with video). *Gastrointest Endosc*. 2016;83:1164–72.
243. Romero-Castro R, Ellrichmann M, Ortiz-Moyano C, Subtil-Inigo JC, Junquera-Florez F, Gornals JB, et al. EUS-guided coil versus cyanoacrylate therapy for the treatment of gastric varices: A multicenter study (with videos). *Gastrointest Endosc*. 2013;78:711–21.
244. Wang ZW, Liu JC, Zhao F, Zhang WG, Duan XH, Chen PF, et al. Comparison of the effects of TIPS versus BRTO on bleeding gastric varices: A meta-analysis. *Can J Gastroenterol Hepatol*. 2020;2020:5143013–9.
245. Wang YB, Zhang JY, Gong JP, Zhang F, Zhao Y. Balloon-occluded retrograde transvenous obliteration versus

- transjugular intrahepatic portosystemic shunt for treatment of gastric varices due to portal hypertension: A meta-analysis. *J Gastroenterol Hepatol.* 2016;31:727–33.
246. Choi YS, Lee JH, Sinn DH, Song YB, Gwak GY, Choi MS, et al. Effect of balloon-occluded retrograde transvenous obliteration on the natural history of coexisting esophageal varices. *J Clin Gastroenterol.* 2008;42:974–9.
 247. Tanihata H, Minamiguchi H, Sato M, Kawai N, Sonomura T, Takasaka I, et al. Changes in portal systemic pressure gradient after balloon-occluded retrograde transvenous obliteration of gastric varices and aggravation of esophageal varices. *Cardiovasc Intervent Radiol.* 2009;32:1209–16.
 248. Procaccini NJ, Al-Osaimi AM, Northup P, Argo C, Caldwell SH. Endoscopic cyanoacrylate versus transjugular intrahepatic portosystemic shunt for gastric variceal bleeding: A single-center U.S. analysis. *Gastrointest Endosc.* 2009;70:881–7.
 249. Saad WE, Darcy MD. Transjugular intrahepatic portosystemic shunt (TIPS) versus balloon-occluded retrograde transvenous obliteration (BRTO) for the management of gastric varices. *Semin Intervent Radiol.* 2011;28:339–49.
 250. Wei B, Zhang L, Tong H, Wang Z, Wu H. Retrospective comparison of clinical outcomes following splenic vein stenting and splenic arterial embolization in sinistral portal hypertension-related gastrointestinal bleeding. *AJR Am J Roentgenol.* 2021; 216:1579–87.
 251. Liu J, Meng J, Yang M, Zhou C, Yang C, Huang S, et al. Two-step complete splenic artery embolization for the management of symptomatic sinistral portal hypertension. *Scand J Gastroenterol.* 2022;57:78–84.
 252. Yipeng W, Cong L, Sizhe W, Chenkai H, Anjiang W, Xuan Z. Effectiveness and safety of endoscopic treatment for duodenal variceal bleeding: A systematic review. *Eur J Gastroenterol Hepatol.* 2021;33:461–9.
 253. Shudo R, Yazaki Y, Sakurai S, Uenishi H, Yamada H, Sugawara K. Clinical study comparing bleeding and non-bleeding rectal varices. *Endoscopy.* 2002;34:189–94.
 254. Maslekar S, Toh EW, Adair R, Bate JP, Botterill I. Systematic review of anorectal varices. *Colorectal Dis.* 2013;15: e702–10.
 255. Kinzel J, Pichetshote N, Dredar S, Aslanian H, Nagar A. Bleeding from a duodenal varix: A unique case of variceal hemostasis achieved using EUS-guided placement of an embolization coil and cyanoacrylate. *J Clin Gastroenterol.* 2014;48:362–4.
 256. Attila T, Kolbeck KJ, Bland ZM, Wang A, Rodriguez SA. Duodenal variceal bleeding successfully treated with transjugular intrahepatic portosystemic shunt: A case report and review of the literature. *Turk J Gastroenterol.* 2008;19: 284–90.
 257. Gunnerson AC, Diehl DL, Nguyen VN, Shellenberger MJ, Blansfield J. Endoscopic duodenal variceal ligation: A series of 4 cases and review of the literature (with video). *Gastrointest Endosc.* 2012;76:900–4.
 258. Pennick MO, Artioukh DY. Management of parastomal varices: Who re-bleeds and who does not? A systematic review of the literature. *Tech Coloproctol.* 2013;17:163–70.
 259. Deipolyi AR, Kalva SP, Oklu R, Walker TG, Wicky S, Ganguli S. Reduction in portal venous pressure by transjugular intrahepatic portosystemic shunt for treatment of hemorrhagic stomal varices. *AJR Am J Roentgenol.* 2014;203: 668–73.
 260. Philips CA, Augustine P. Endoscopic ultrasound-guided management of bleeding rectal varices. *ACG Case Rep J.* 2017;4:e101.
 261. Vangeli M, Patch D, Terreni N, Tibballs J, Watkinson A, Davies N, et al. Bleeding ectopic varices—treatment with transjugular intrahepatic porto-systemic shunt (TIPS) and embolisation. *J Hepatol.* 2004;41:560–6.
 262. McCormack TT, Sims J, Eyre-Brook I, Kennedy H, Goepel J, Johnson AG, et al. Gastric lesions in portal hypertension: inflammatory gastritis or congestive gastropathy? *Gut.* 1985;26: 1226–32.
 263. Panés J, Bordas JM, Piqué JM, Bosch J, García-Pagán JC, Feu F, et al. Increased gastric mucosal perfusion in cirrhotic patients with portal hypertensive gastropathy. *Gastroenterology.* 1992;103:1875–82.
 264. Spina GP, Arcidiacono R, Bosch J, Pagliaro L, Burroughs AK, Santambrogio R, et al. Gastric endoscopic features in portal hypertension: Final report of a consensus conference, Milan, Italy, September 19, 1992. *J Hepatol.* 1994;21(3):461–7.
 265. Sarin S. Diagnostic issue: Portal hypertensive gastropathy and gastric varices. In: DeFranchis R, ed. *Portal hypertension II. Proceedings of the Second Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies.* Oxford: Blackwell Science, 1996. 30–55.
 266. Fontana RJ, Sanyal AJ, Ghany MG, Bonkovsky HL, Morgan TR, Litman HJ, et al. Development and progression of portal hypertensive gastropathy in patients with chronic hepatitis C. *Am J Gastroenterol.* 2011;106:884–93.
 267. Carpinelli L, Primignani M, Preatoni P, Angeli P, Battaglia G, Beretta L, et al. Portal hypertensive gastropathy: Reproducibility of a classification, prevalence of elementary lesions, sensitivity and specificity in the diagnosis of cirrhosis of the liver. A NIEC multicentre study. *New Italian Endoscopic Club. Ital J Gastroenterol Hepatol.* 1997;29:533–40.
 268. Primignani M, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A, et al. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). *Gastroenterology.* 2000;119:181–7.
 269. Merli M, Nicolini G, Angeloni S, Gentili F, Attili AF, Riggio O. The natural history of portal hypertensive gastropathy in patients with liver cirrhosis and mild portal hypertension. *Am J Gastroenterol.* 2004;99:1959–65.
 270. Kumar A, Mishra SR, Sharma P, Sharma BC, Sarin SK. Clinical, laboratory, and hemodynamic parameters in portal hypertensive gastropathy: A study of 254 cirrhotics. *J Clin Gastroenterol.* 2010;44:294–300.
 271. Merkel C, Schipilliti M, Bighin R, Bellini B, Angeli P, Bolognesi M, et al. Portal hypertension and portal hypertensive gastropathy in patients with liver cirrhosis: A haemodynamic study. *Dig Liver Dis.* 2003;35:269–74.
 272. Davern TJ, Chalasani N, Fontana RJ, Hayashi PH, Protiva P, Kleiner DE, et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology.* 2011;141:1665–72.e9.
 273. Sarin SK, Shahi HM, Jain M, Jain AK, Issar SK, Murthy NS. The natural history of portal hypertensive gastropathy: Influence of variceal eradication. *Am J Gastroenterol.* 2000; 95:2888–93.
 274. Lo GH, Lai KH, Cheng JS, Hsu PI, Chen TA, Wang EM, et al. The effects of endoscopic variceal ligation and propranolol on portal hypertensive gastropathy: A prospective, controlled trial. *Gastrointest Endosc.* 2001;53:579–84.
 275. Zhou Y, Qiao L, Wu J, Hu H, Xu C. Comparison of the efficacy of octreotide, vasopressin, and omeprazole in the control of acute bleeding in patients with portal hypertensive gastropathy: A controlled study. *J Gastroenterol Hepatol.* 2002;17: 973–9.
 276. Kouroumalis EA, Koutroubakis IE, Manousos ON. Somatostatin for acute severe bleeding from portal hypertensive gastropathy. *Eur J Gastroenterol Hepatol.* 1998;10:509–12.
 277. Panés J, Bordas JM, Piqué JM, García-Pagán JC, Feu F, Terés J, et al. Effects of propranolol on gastric mucosal perfusion in cirrhotic patients with portal hypertensive gastropathy. *Hepatology.* 1993;17:213–8.

278. Shigemori H, Iwao T, Ikegami M, Toyonaga A, Tanikawa K. Effects of propranolol on gastric mucosal perfusion and serum gastrin level in cirrhotic patients with portal hypertensive gastropathy. *Dig Dis Sci*. 1994;39:2433–8.
279. Hosking SW, Kennedy HJ, Seddon I, Triger DR. The role of propranolol in congestive gastropathy of portal hypertension. *Hepatology*. 1987;7:437–41.
280. Conn HO, Grace ND, Bosch J, Groszmann RJ, Rodés J, Wright SC, et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: A multicenter, randomized clinical trial. The Boston-New Haven-Barcelona Portal Hypertension Study Group. *Hepatology*. 1991;13:902–12.
281. Merkel C, Marin R, Sacerdoti D, Donada C, Cavallarin G, Torboli P, et al. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology*. 2000;31:324–9.
282. Pérez-Ayuso RM, Piqué JM, Bosch J, Panés J, González A, Pérez R, et al. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. *Lancet*. 1991;337:1431–4.
283. Rockey DC. An update: Portal hypertensive gastropathy and colopathy. *Clin Liver Dis*. 2019;23:643–58.
284. D'Amico G, Montalbano L, Traina M, Pisa R, Menozzi M, Spanò C, et al. Natural history of congestive gastropathy in cirrhosis. The Liver Study Group of V. Cervello Hospital. *Gastroenterology*. 1990;99:1558–64.
285. El Shahawy MS, Shady ZM, Gaafar A. The efficacy of argon plasma coagulation versus carvedilol for treatment of portal hypertensive gastropathy. *Digestion*. 2020;101:651–8.
286. Hashim AE, Zaky S, Berengy MS, Emran T, Hegazy M. Effect of endoscopic argon plasma coagulation on gastrointestinal blood loss due to portal hypertensive gastropathy. *J Clin Gastroenterol Hepatol*. 2017;1:9.
287. Herrera S, Bordas JM, Llach J, Ginès A, Pellisé M, Fernández-Esparrach G, et al. The beneficial effects of argon plasma coagulation in the management of different types of gastric vascular ectasia lesions in patients admitted for GI hemorrhage. *Gastrointest Endosc*. 2008;68:440–6.
288. Bansal RK, Gupta MK, Gupta VK, Kaur G, Seth AK. Endoscopic treatment of upper gastrointestinal bleeding using haemoseal spray: A retrospective, observational study from a tertiary center in North India. *J Dig Endosc*. 2020;11:279–82.
289. Gonzalez PS, Villanueva C, Mones J, Boadas J, Oliva E, Balanzo J. Derivación portosistémica en el tratamiento de la gastropatía por hipertensión portal. *Med Clin (Barc)*. 1991;97:741–3.
290. Kamath PS, Lacerda M, Ahlquist DA, McKusick MA, Andrews JC, Nagorney DA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. *Gastroenterology*. 2000;118:905–11.
291. Lemmers A, Evrard S, Demetter P, Verset G, Gossum AV, Adler M, et al. Gastrointestinal polypoid lesions: A poorly known endoscopic feature of portal hypertension. *United European Gastroenterol J*. 2014;2:189–96.
292. Kara D, Hüsing-Kabar A, Schmidt H, Grünwald I, Chandhok G, Maschmeier M, et al. Portal hypertensive polyposis in advanced liver cirrhosis: The unknown entity? *Can J Gastroenterol Hepatol*. 2018;2018:2182784–7.
293. Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol*. 2008;26:2992–8.
294. Barone C, Basso M, Biolato M, Pompili M, Rufini V, Miele L, et al. A phase II study of sunitinib in advanced hepatocellular carcinoma. *Dig Liver Dis*. 2013;45:692–8.
295. D'Alessio A, Fulgenzi CAM, Nishida N, Schönlein M, von Felden J, Schulze K, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: A real-world study. *Hepatology*. 2022;76:1000–12.
296. Iavarone M, Primignani M, Vavassori S, Sangiovanni A, La Mura V, Romeo R, et al. Determinants of esophageal varices bleeding in patients with advanced hepatocellular carcinoma treated with sorafenib. *United European Gastroenterol J*. 2016;4:363–70.
297. Lim J, Kim HI, Kim E, Kim J, An J, Chang S, et al. Variceal bleeding is aggravated by portal venous invasion of hepatocellular carcinoma: A matched nested case-control study. *BMC Cancer*. 2021;21:11.
298. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. For the IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–905.
299. TECENTRIQ (atezolizumab) injection, for intravenous use [package insert]. South San Francisco, CA: Genentech; 2020.
300. Ripoll C, Genesca J, Araujo IK, Graupera I, Augustin S, Tejedor M, et al. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study. *Hepatology*. 2013;58:2079–88.
301. Sarkar M, Brady CW, Fleckenstein J, Forde KA, Khungar V, Molleston JP, et al. Reproductive health and liver disease: Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;73:318–65.
302. Stelmach A, Slowik Ł, Cichoń B, Lemm M, Poński M, Kaszuba M, et al. Esophageal varices during pregnancy in the course of cirrhosis. *Eur Rev Med Pharmacol Sci*. 2020;24:9615–7.
303. Ingraham CR, Padia SA, Johnson GE, Easterling TR, Liou IW, Kanal KM, et al. Transjugular intrahepatic portosystemic shunt placement during pregnancy: A case series of five patients. *Cardiovasc Intervent Radiol*. 2015;38:1205–10.
304. Tanaka K, Tanaka H, Kamiya C, Katsuragi S, Sawada M, Tsuritani M, et al. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. *Circ J*. 2016;80:2221–6.
305. Sack JS, Li M, Zucker SD. Bleeding outcomes following transesophageal echocardiography in patients with cirrhosis and esophageal varices. *Hepatol Commun*. 2021;5:283–92.
306. Hui RW, Leung CM. Incidence of gastrointestinal bleeding after transesophageal echocardiography in patients with gastroesophageal varices: A systematic review and meta-analysis. *J Am Soc Echocardiogr*. 2022;35:387–94.
307. Odewole M, Sen A, Okoruwa E, Lieber SR, Cotter TG, Nguyen AD, et al. Systematic review with meta-analysis: Incidence of variceal hemorrhage in patients with cirrhosis undergoing transesophageal echocardiography. *Aliment Pharmacol Ther*. 2022;55:1088–98.
308. Chang J, Höfer P, Böhlng N, Lingohr P, Manekeller S, Kalff JC, et al. Preoperative TIPS prevents the development of postoperative acute-on-chronic liver failure in patients with high CLIF-C AD score. *JHEP Rep*. 2022;4:100442.

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