# ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation

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**Disorders of the mesenteric, portal, and hepatic veins and mesenteric and hepatic arteries have important clinical consequences and may lead to acute liver failure, chronic liver disease, noncirrhotic portal hypertension, cirrhosis, and hepatocellular carcinoma. Although literature in the field of vascular liver disorders is scant, these disorders are common in clinical practice, and general practitioners, gastroenterologists, and hepatologists may benefit from expert guidance and recommendations for management of these conditions. These guidelines represent the official practice recommendations of the American College of Gastroenterology. Key concept statements based on author expert opinion and review of literature and specific recommendations based on PICO/GRADE analysis have been developed to aid in the management of vascular liver disorders. These recommendations and guidelines should be tailored to individual patients and circumstances in routine clinical practice.**

*Am J Gastroenterol 2020;115:18–40. https://doi.org/10.14309/ajg.0000000000000486; published online January 3, 2020*

## INTRODUCTION

The blood supply to the liver is unique with about 75% of blood inflow coming through the portal vein and the remaining 25% through the hepatic artery. The portal venous system carries capillary blood from the entire gastrointestinal (GI) tract (except for the upper esophagus and distal rectum), pancreas, gallbladder, and spleen to the liver (Figure 1). The portal vein is formed behind the neck of the pancreas by the confluence of the splenic vein and the superior mesenteric vein. The inferior mesenteric vein usually drains into the splenic vein, whereas the left gastric vein drains at the confluence of the portal, splenic, and superior mesenteric veins. The portal vein, approximately 6–8 cm in length and 1 cm in diameter, divides in the hilum of the liver into the left and right portal vein branches. Portal blood drains into hepatic sinusoids which drain into the inferior vena cava (IVC) through the hepatic veins. The major hepatic veins are the right, middle, and left hepatic veins. The left and middle hepatic veins usually join within the liver entering the left side of the IVC as a single vessel and separate from but adjacent to the right hepatic vein.

Vascular liver disorders of the mesenteric, portal, and hepatic veins and mesenteric and hepatic arteries have important clinical consequences and may lead to acute liver failure, chronic liver disease, noncirrhotic portal hypertension (PH), cirrhosis, and hepatocellular carcinoma (HCC). Furthermore, these disorders play an important role as precipitating factors for the development and progression of complications in patients with existing chronic liver diseases. Literature in the field of vascular liver disorders is restricted predominantly to nonrandomized, observational data, which negatively impacts the quality of evidence for the development of guidelines or recommendations. However, vascular liver disorders are common in clinical practice, and general practitioners, gastroenterologists, and hepatologists may benefit from expert guidance in managing these patients.

The authors were invited by the American College of Gastroenterology to develop this practice guideline document on vascular disorders of the liver using the best currently available evidence. The discussion will be confined to thrombotic and bleeding risk in cirrhosis; portal and hepatic venous thrombosis; hereditary hemorrhagic telangiectasia (HHT) involving the liver; and mesenteric arterial aneurysms.

Specific recommendations based on patient, intervention, comparator, outcome (PICO)/Grading of Recommendations Assessment, Development, and Evaluation (GRADE) analysis are presented in Table 1. Key concepts on vascular liver disorders are presented in Table 2. It is the suggestion of the authors that these recommendations and guidelines be used only as a framework to make decisions in routine clinical practice. The authors also recognize that the lack of high-quality evidence in this field may lead to variation in practice recommendations among specialties.

To develop these guidelines, a search was performed on the Ovid search platform: Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Evidence-Based Medicine Reviews—Cochrane Central Registry of Controlled Trials, EMBASE, and PsycInfo for the period 2000 through 2018 and limited to the English language. A combination of database-specific subject headings (subject's headings plus text words) was used (see Table 1, Supplementary

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**Received March 13, 2019; accepted August 28, 2019**

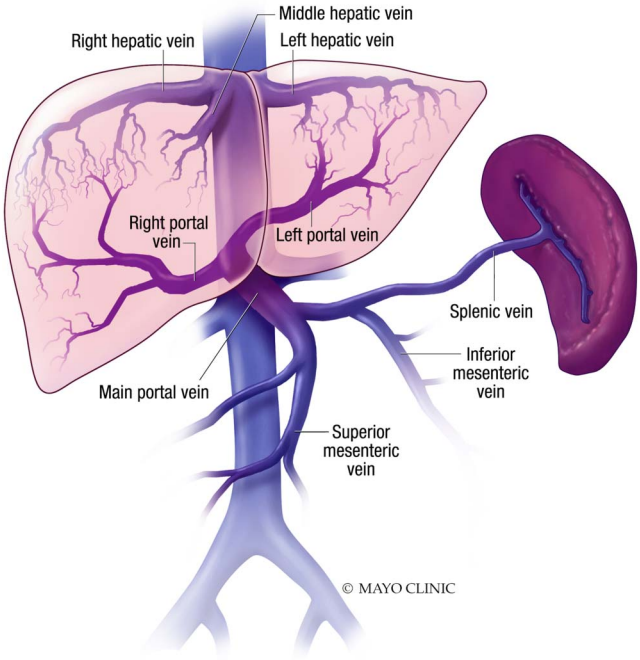


**Figure 1.** Hepatic and portal venous system.

Digital Content 1, http://links.lww.com/AJG/B338). The results were downloaded from each database into EndNote X7, and duplicates were removed.

To evaluate the level of evidence and strength of recommendations, we used the GRADE system, as suggested by the practice guideline committee of the college. The strength of recommendation is graded as strong or conditional as a consensus among the authors, considering the weight of desirable and undesirable effects of intervention. The level of evidence was determined independently of the authors and designated as high, moderate, low, and very low, based on the current literature.

## BLEEDING AND THROMBOTIC RISK IN CIRRHOSIS

A growing body of evidence shows that hemostatic pathways in compensated cirrhosis are largely intact, but in a precarious balance that can shift in either direction (1). Increased clotting risk is evidenced by portal vein thrombosis (PVT) and peripheral deep venous thrombosis. Bleeding risk seems to be due to accelerated intravascular coagulation and fibrinolysis (AICF) involving premature clot dissolution. However, more common forms of bleeding such as variceal hemorrhage have only a tenuous relationship to the clotting cascade being instead driven by portal venous pressure and infection.

### Recent concepts in normal hemostatic pathways

The discovery of the role of factor VII in normal hemostasis has led to several conceptual changes in our understanding of hemostatic pathways and to the emergence of the cell-based model of clot formation with less emphasis on the classic "intrinsic" and "extrinsic" mechanisms (Figure 2) (2). Hemostasis involves several coagulation products and the integrity of multiple systems. These include but are not limited to the liver, platelets, and endothelium. The liver plays a paramount role in coagulation because it (i) produces coagulation factors (factor VII and intrinsic and extrinsic pathway factors) and coagulation inhibitors (protein C [PC] and S and antithrombin); (ii) clears these factors by synthesizing plasminogen; and (iii) synthesizes thrombopoietin (TPO) to stimulate the production of platelets from megakaryocytes in the bone marrow. The role of platelets in hemostasis is the formation of a platelet plug, a primary hemostasis process promoted by endothelium-derived von Willebrand factor (vWF). VWF is cleaved by a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, an enzyme produced in the liver to counterbalance its effect and help in dissolution of the clot. Clot dissolution also requires the activation of plasminogen to plasmin and the binding of thrombomodulin secreted in endothelial cells to thrombin. This leads to fibrinolysis and activation of PC which are some of the final steps in the dissolution of the clot.

The net balance of procoagulant and anticoagulant factor pathways governs whether there is propagation or abortion of a protective or pathological clot which is then further governed by the simultaneously activated thrombolytic (fibrinolytic) plasmin-based pathways which govern clot remodeling and/or clot dissolution (3,4).

### Alterations in the hemostatic pathways in cirrhosis

The deficit of liver-derived procoagulant factors in cirrhosis is well known, but the deficit of liver-derived anticoagulants such as PC and the increases in endothelial-derived factors such as factor VIII and vWF are less well appreciated. The magnitude of deficient PC in cirrhosis has become evident through studies of thrombin (factor II) generation in the presence of the endothelial-derived cofactor thrombomodulin. Together with increased factor VIII and vWF, these changes can result in a relative hypercoagulable state in cirrhotic patients. The magnitude of the PC deficit, in terms of diminished control of thrombin generation, may be as high as seen in congenital PC deficiency (5).

Factors governing clot structure, whether venous or arterial, include the amount of circulating fibrinogen and its molecular structure, the presence of cellular components, the microenvironment of cofactors/inhibitors, and flow rates. Most fibrinogen is synthesized in the liver with a circulating half-life of 3–5 days. Fibrinogen levels are often maintained even in advanced liver disease, although very low levels below 100 mg/dL can be seen with states of hyperfibrinolysis and are associated with prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT). Thrombocytopenia due to hypersplenism is also common and problematic, although bleeding risk is in part offset by increased vWF-related changes in endothelial function (6). Further key changes are found in the fibrinolytic system which governs clot remodeling. Although the mechanisms continue to be debated, fibrinolytic capacity is clearly increased in cirrhosis and may tip over into a state of hyperfibrinolysis associated with mucosal and wound bleeding (7). These changes observed in patients with cirrhosis are usually in balance; however, clinical deterioration results in loss of this balance, leading to bleeding, inappropriate clotting, or sometimes both processes at once.

**Table 1. Recommendations and PICO questions on management of vascular diseases of the liver**

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| **Bleeding and thrombotic risk in liver disorders** |
| 1. In patients with cirrhosis, does prophylactic infusion of 2 or more units of FFP reduce the risk of bleeding?<br>We do not recommend FFP to improve thrombin generation in patients with cirrhosis at conventional doses (10 mL/kg). If sufficient volume is given (1–2 L) to lower a significantly prolonged INR, volume expansion increases portal pressure and may trigger variceal hemorrhage. Thus in most situations, infusion of plasma prophylactically to decrease bleeding risk is futile and potentially risky (conditional recommendation, low level of evidence). |
| 2. In patients with cirrhosis with platelet count <50,000/mL, is correction of platelet count to >50,000/mL associated with reduced risk of bleeding compared with patients with platelet count <50,000/mL?<br>We do not recommend prophylactic platelet transfusions before common procedures such as routine variceal banding or paracentesis outside of significant renal dysfunction (serum creatinine > 2.5 mg/dL) or sepsis. Existing data indicate a somewhat tenuous relationship between bleeding risk and platelet count. *In vitro* studies demonstrate adequate thrombin production with platelet levels ≥50,000/mL. Infusion of a single adult platelet dose does not improve thrombin generation. Higher platelet levels may be more appropriate for high-risk procedures such as removal of large polyps and major surgery, but will probably require higher doses of platelet infusions; if the procedure is elective, the use of TPO agonists may be more appropriate (conditional recommendation, very low level of evidence). |
| 3. In patients with cirrhosis and persistent active bleeding, are antifibrinolytic agents effective in reducing bleeding compared with no treatment?<br>We do not recommend antifibrinolytic agents such as epsilon aminocaproic acid and tranexamic acid to reduce bleeding in the absence of hyperfibrinolysis. These agents are not generally considered to induce a hypercoagulable state but require caution if pathological clot such as PVT is already present (conditional recommendation, very low level of evidence). |
| **Portal and mesenteric vein thrombosis in patients with and without cirrhosis** |
| 4. Should Doppler US, CT scan, or MRI be performed for diagnosis of portal and/or mesenteric vein thrombosis?<br>We recommend Doppler ultrasound examination as the initial noninvasive modality for diagnosis of PVT. Contrast-enhanced CT or MRI scan is recommended to assess the extension of thrombus into the mesenteric veins and to exclude tumor thrombus among patients with cirrhosis who develop new portal and/or mesenteric vein thrombus (strong recommendation, very low level of evidence). |
| **Portal or mesenteric vein thrombosis in the absence of cirrhosis** |
| 5. Should anticoagulation be preferred to thrombolytic therapy as the first strategy in the management of acute portal or mesenteric vein thrombosis?<br>We recommend anticoagulation for all noncirrhotic patients with acute symptomatic portal or mesenteric vein thrombosis in the absence of any contraindication (strong recommendation, low level of evidence). |
| 6. Should patients with chronic PVT be treated with anticoagulation or observed?<br>We suggest anticoagulation for patients with chronic PVT if there is (i) evidence of inherited or acquired thrombophilia, (ii) progression of thrombus into the mesenteric veins, or (iii) current or previous evidence of bowel ischemia (conditional recommendation, very low level of evidence). |
| 7. In patients with acute symptomatic portal or mesenteric vein thrombosis without a demonstrable thrombophilia, should anticoagulation be administered for 6 months or indefinitely?<br>We suggest at least 6 months of anticoagulation in patients with portal or mesenteric vein thrombosis without a demonstrable thrombophilia and when the etiology of the thrombosis is reversible. Indefinite anticoagulation is recommended in patients with portal or mesenteric vein thrombosis and thrombophilia (conditional recommendation, very low level of evidence). |
| 8. Should beta-blockers or endoscopic variceal band ligation be used for primary variceal bleeding prophylaxis in noncirrhotic patients with chronic PVT who require anticoagulation?<br>We recommend nonselective beta-blockers for prevention of variceal bleeding in patients with high-risk varices and portal and/or mesenteric vein thrombosis requiring anticoagulation. Endoscopic variceal ligation may be performed if there are contraindications or intolerance to beta-blockers; however, anticoagulation may need to be interrupted in the periprocedural period (strong recommendation, low quality of evidence). |
| 9. Should unfractionated heparin or LMWH be used as the initial agent for anticoagulation among patients with portal and/or MVT?<br>We suggest either unfractionated heparin or LMWH be used once a decision is made to initiate anticoagulation for treatment of portal and/or MVT. However, pros and cons of either approach should be considered before initiating either regimen (conditional recommendation, very low level of evidence). |
| 10. Should LMWH or warfarin or direct-acting thrombin or factor Xa inhibitors be used for maintenance of anticoagulation?<br>We suggest either LMWH or warfarin be used. Although this field continues to evolve, there is currently only limited experience with DOACs, which includes Xa or thrombin inhibitors. Because absorption of these agents may be limited in the presence of intestinal edema, some monitoring of therapy is recommended. A normal thrombin time and aPTT for dabigatran and a normal prothrombin time or anti-Xa activity for apixaban and rivaroxaban rule out substantial drug effect. Pros and cons of all approaches including availability of reversal agents should be considered before deciding on the specific regimen (conditional recommendation, very low level of evidence). |
| **Portal or mesenteric vein thrombosis with cirrhosis** |
| 11. Should anticoagulation be preferred to thrombolytic therapy or no therapy as the first strategy in the management of acute portal or mesenteric vein thrombosis in patients with cirrhosis?<br>We recommend anticoagulation for patients with (i) acute complete main PVT, (ii) MVT, or (iii) extension of portal venous thrombosis into mesenteric veins. Risk of bleeding must be weighed against benefits as for example, in patients with platelets <50,000/μL or hepatic encephalopathy at risk of falls (strong recommendation, low level of evidence). |

**Table 1. (*continued*)**

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| 12. Should patients with cirrhosis and chronic PVT be treated with anticoagulation or observed?<br>We suggest anticoagulation in patients with chronic PVT only if there is (i) evidence of inherited thrombophilia, (ii) progression of thrombus, or (iii) history of bowel ischemia due to thrombus extension into the mesenteric veins. Anticoagulation may also be considered in patients awaiting LT (conditional recommendation, very low level of evidence). |
| 13. In patients with acute portal or mesenteric vein thrombosis and cirrhosis without an inherited thrombophilia, should anticoagulation be administered for 6 months or continued indefinitely?<br>We suggest 6 months of anticoagulation in patients with cirrhosis and acute portal or MVT. Anticoagulation is continued beyond this period in patients with portal or mesenteric vein thrombosis who are on the waiting list for liver transplant (conditional recommendation, very low level of evidence). |
| 14. Should beta-blockers or endoscopic variceal ligation be used for variceal bleeding prophylaxis in patients with cirrhosis and either acute or chronic PVT who require anticoagulation?<br>We recommend nonselective beta-blockers for primary prevention of variceal bleeding in cirrhotic patients with high-risk varices and portal and/or mesenteric vein thrombosis requiring anticoagulation. Endoscopic variceal ligation may be performed if there is a contraindication to or intolerance to beta-blockers; however, anticoagulation may need to be interrupted in the periprocedural period (strong recommendation, low quality of evidence). |
| 15. Should unfractionated heparin vs LMWH be used as the initial agent for anticoagulation among patients with cirrhosis and acute portal and/or MVT?<br>We suggest either unfractionated heparin or LMWH for treatment of portal and/or MVT once a decision is made to initiate anticoagulation. Unfractionated heparin is preferred in the presence of renal insufficiency, and LMWH is preferred in the presence of thrombocytopenia (conditional recommendation, very low level of evidence). |
| **Budd-Chiari Syndrome** |
| 16. Should Doppler US, contrast-enhanced CT scan, or MRI be obtained to diagnose BCS in patients with new-onset ascites?<br>We recommend Doppler US as the initial diagnostic test for evaluation for BCS. Contrast-enhanced CT or MRI scans should be obtained to assess thrombus extension, rule out tumor thrombus, determine response to anticoagulation therapy, evaluate indeterminate hepatic nodules, and whenever there is high clinical suspicion of BCS despite negative or inconclusive Doppler US results (conditional recommendation, low level of evidence). |
| 17. Should anticoagulation or interventional radiology treatment with angioplasty or TIPS be the initial treatment of choice for patients with BCS?<br>We recommend stepwise management from least to most invasive therapies for patients with BCS. Systemic anticoagulation is the initial treatment of choice. If medical therapy fails, as determined by worsening liver and/or renal function, ascites, or hepatic encephalopathy, then endovascular therapies such as angioplasty or TIPS are recommended. LT is reserved for TIPS failure and BCS presenting as fulminant liver failure (strong recommendation, moderate level of evidence). |
| 18. Should patients with chronic BCS undergo HCC surveillance vs no surveillance?<br>We suggest surveillance for HCC with abdominal ultrasound and serum AFP levels every 6 mo in patients with chronic BCS. Diagnosis of HCC is challenging, and patients are best referred to centers of expertise for diagnosis (conditional recommendation, low level of evidence). |
| **Mesenteric artery aneurysms** |
| 19. Should asymptomatic mesenteric artery aneurysms <2 cm in diameter be observed or treated?<br>We suggest treatment in asymptomatic patients only with aneurysms of the pancreaticoduodenal and gastroduodenal arcade, intraparenchymal hepatic artery branches, women of childbearing age, and recipients of a liver transplant, irrespective of aneurysm diameter. In asymptomatic patients with mesenteric aneurysms <2 cm in diameter and not meeting the aforesaid criteria, follow-up imaging is recommended initially in 6 mo, then at 1 yr and subsequently every 1–2 yr. We recommend that mesenteric artery aneurysms associated with symptoms (abdominal pain in the absence of other causes) be treated (conditional recommendation, low level of evidence). |
| 20. Should asymptomatic mesenteric artery aneurysms >2 cm in diameter be observed or treated?<br>We recommend intervention for all aneurysms >2 cm in diameter even when asymptomatic (strong recommendation, low level of evidence). |
| **Hereditary hemorrhagic telangiectasia** |
| 21. Is screening for LVMs in patients with HHT associated with better outcomes?<br>We do not recommend routine screening for LVMs in patients with HHT. There is no evidence to suggest that making a diagnosis in an asymptomatic patient has clinical benefits or prevents death. However, those with a liver bruit, hyperdynamic circulation, or liver test abnormalities should be further evaluated for LVMs. Of note, women with HHT and LVMs who become pregnant warrant special attention due to anticipated hemodynamic stress (strong recommendation, low level of evidence). |
| 22. Should Doppler US or CT/MRI scan be performed for diagnosis of LVMs in patients with HHT and symptoms suggestive of LVMs?<br>We suggest contrast CT scan or MRI/MRCP in patients with HHT who develop symptoms/signs of heart failure, biliary ischemia, hepatic encephalopathy, mesenteric ischemia, or PH. Doppler US may establish a diagnosis of LVMs in patients with HHT and a compatible clinical picture, but is less accurate than CT scan or MRI/MRCP. Angiography and/or liver biopsy are not recommended in the diagnosis of LVMs (strong recommendation, low level of evidence). |

**Table 1. (*continued*)**

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| 23. In patients with HHT and symptomatic LVMs, is bevacizumab more effective in resolving symptoms and/or avoiding invasive therapies (HA embolization/transplant) than standard therapies?<br>We recommend standard medical therapy for each complication of liver VMs in patients with HHT, which results in symptom resolution in the majority. In nonresponders to standard therapy, management should be undertaken at specialized centers using a multidisciplinary approach. Bevacizumab should be considered in patients with HOHF and possibly for other complications of LVM before using invasive therapies, although not all patients respond. Symptoms recur after treatment discontinuation, and bevacizumab can be associated with significant side effects. Transarterial hepatic artery embolization or surgical ligation is proscribed in patients with biliary involvement or PH, and there is insufficient evidence to recommend its use in HOHF. Liver transplant is an important option for nonresponders to standard treatment or patients who relapse after medical treatment, but criteria for listing are not clearly defined, the procedure may be associated with a high rate of perioperative complications, and liver VMs may recur as early as 6 yr after transplant (conditional recommendation, low level of evidence). |

aPTT, activated partial thromboplastin time; AFP, alpha-fetoprotein; BCS, Budd-Chiari syndrome; CT, computed tomography; DOAC, direct oral anticoagulants; FFP, fresh-frozen plasma; HCC, hepatocellular carcinoma; HHT, hereditary hemorrhagic telangiectasia; HOHF, high-output heart failure; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LT, liver transplantation; LVM, liver vascular malformation; MRCP, magnetic resonance cholangiogram; MRI, magnetic resonance imaging; MVT, mesenteric venous thrombosis; PICO, patient/intervention/comparator/outcome; PH, portal hypertension; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; TPO, thrombopoietin.

***Key concepts***

1. Current evidence shows that hemostatic pathways in compensated cirrhosis are largely intact but in a precarious balance. Sepsis, hypothermia, or kidney dysfunction can shift the balance in either direction toward inappropriate clotting or bleeding particularly in the decompensated stage.
2. The deficit of liver-derived procoagulant factors in cirrhosis is offset by the deficit of liver-derived anticoagulants PC and increased endothelial-derived factor VIII and vWF.
3. Changes in the anticoagulant system in cirrhosis can cause relative hypercoagulability that are not detected by conventional tests of hemostasis.

## Assessment of bleeding risk in cirrhosis

There is poor correlation between international normalized ratio (INR) and thrombin production in cirrhosis (8). In addition, INR was developed specifically as a marker of anticoagulant activity of vitamin K antagonists (VKAs). The mathematical derivation of INR from the PT depends on the international sensitivity index (ISI) of the various commercially available thromboplastins used as a reagent in the PT test (9–11). The ISI is derived from a panel of VKA-treated patients to provide a reference standard. Great variation in the ISI, and thus the INR, has been demonstrated in cirrhotic patients, a reflection of the thromboplastin used. A novel test called the liver INR has been proposed, wherein the ISI for a given thromboplastin is calculated against a cirrhosis-based reference panel. However, the test is not widely available and is unlikely to provide a significant clinical advantage, given limitations of PT as a predictor of bleeding or clotting (12–15). Whole blood viscoelastic tests, thromboelastography, and rotational thromboelastometry (ROTEM) provide a more comprehensive assessment of the hemostatic balance because they measure the rise in viscosity as fibrin clot forms and the decline in viscosity as the fibrin clot is broken down by the fibrinolytic system. These tests are most useful to demonstrate intact pathways when conventional tests such as INR are prolonged; however, they lack well-defined "cutoffs" for clinical outcomes. Furthermore, viscoelastic tests are not yet widely used.

Using INR as a target for "correction" to decrease bleeding risk in cirrhosis has been a common practice. In 1 survey of blood product use over a 6-week period, cirrhotic patients constituted 7% of the total of 168 patients receiving either plasma or platelets but consumed 34% of the plasma transfused, mostly as INR-guided prophylaxis (16). In addition to the lack of a physiological basis in cirrhosis, as reviewed above, this practice is problematic for several reasons. First, fresh-frozen plasma (FFP), commonly given as 2–4 units, is rarely able to achieve a target INR of 1.5 or less (17). In fact, the plasma volume needed to reach a goal of 1.5 is remarkably high and may be on the order of liters (18). Moreover, *in vitro* studies of human samples have shown that mixing plasma at an equivalent dose of 10 mL/kg can lower the PT but does not enhance thrombin production (19). Most importantly, however, intraoperative studies performed in a previous era among patients undergoing portosystemic shunt surgery for variceal bleeding have demonstrated that rapid volume expansion was linearly related to directly measured increments in portal pressure (20). The extent of portal pressure increase with high volume plasma infusion has been estimated to be in the range of 15–20 mm Hg (21–23). This relationship is supported by liver transplant studies reporting the efficacy of intraoperative phlebotomy in reducing portal pressure and by experimental studies showing the adverse effect of aggressive volume restitution on bleeding risk in animal models of cirrhosis (24). Thus, FFP infusion to "correct" the INR may paradoxically increase the bleeding risk of cirrhotic patients with PH. Finally, performance of invasive procedures, such as large volume paracentesis, without prophylactic FFP administration in outpatients with cirrhosis and prolonged prothrombin time has been shown to be safe, even in patients with INR as high as 8.7 (25,26).

***Key concepts***

4. INR correlates poorly with thrombin generation and risk of bleeding in patients with cirrhosis.

***Recommendations***

1. In patients with cirrhosis, does prophylactic infusion of 2 or more units of FFP reduce the risk of bleeding?
   We do not recommend FFP to improve thrombin generation in patients with cirrhosis at conventional doses (10 mL/kg). If sufficient volume is given (1–2 L) to lower a significantly prolonged INR, volume expansion increases portal pressure and may trigger variceal hemorrhage. Thus, in most situations, infusion of plasma prophylactically to decrease bleeding risk is futile and potentially risky (conditional recommendation, low level of evidence).

**Table 2. Key concepts and statements on the management of vascular liver disorders**

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| **Bleeding and thrombotic risk in cirrhosis** |
| 1. Current evidence shows that hemostatic pathways in compensated cirrhosis are largely intact but in a precarious balance. Sepsis, hypothermia, or kidney dysfunction can shift the balance in either direction toward inappropriate clotting or bleeding particularly in the decompensated stage. |
| 2. The deficit of liver-derived procoagulant factors in cirrhosis is offset by the deficit of liver-derived anticoagulants PC and increased endothelial-derived factor VIII and vWF. |
| 3. Changes in the anticoagulant system in cirrhosis can cause relative hypercoagulability that are not detected by conventional tests of hemostasis. |
| 4. INR correlates poorly with thrombin generation and risk of bleeding in patients with cirrhosis. |
| 5. Whole blood viscoelastic tests (TEG and ROTEM) may be useful to avoid unnecessary use of blood products before invasive procedures in patients with cirrhosis and prolonged INR. However, further studies are needed to establish specific parameters for blood product use in this population. |
| 6. Pharmacologic prophylaxis against DVT seems to be safe in hospitalized cirrhotic patients in the absence of bleeding or platelet counts less than 50,000/μL. |
| **Portal and mesenteric vein thrombosis in patients with and without cirrhosis** |
| 7. Investigation for thrombophilia should be performed for portal and/or mesenteric vein thrombosis among patients without cirrhosis in the absence of obvious etiology such as an acute intraabdominal process. Among patients with cirrhosis, thrombophilia work-up is performed among patients with portal and/or mesenteric vein thrombosis when there is (i) previous history of thrombosis, (ii) thrombosis at unusual sites such as hepatic veins, and (iii) family history of thrombosis. |
| 8. *JAK2* mutation testing should be obtained for evaluation of underlying myeloproliferative neoplasms, the most common thrombophilic etiology for portal and/or mesenteric vein thrombosis in the absence of cirrhosis. |
| 9. Abdominal pain disproportionate to physical findings on abdominal examination should raise suspicion for portal and/or MVT. |
| 10. Among patients with portal and/or MVT, intestinal ischemia is suspected with the development of fever, ascites, rebound abdominal tenderness, leukocytosis, and elevated serum lactate levels. |
| 11. Doppler ultrasound examination of the hepatic vasculature should be obtained in patients with (i) new diagnosis of cirrhosis, (ii) onset of PH, or (iii) hepatic decompensation. |
| 12. Endoscopic evaluation should be performed in patients with chronic PVT to assess for esophageal and/or gastric varices. |
| 13. More data are needed before implementing routine use of prophylactic anticoagulation for prevention of PVT in patients with cirrhosis. |
| 14. Anticoagulation among patients with cirrhosis and portal and/or mesenteric vein thrombosis is not associated with increased risk of variceal bleeding. |
| 15. Endoscopic treatment of portal hypertensive cholangiopathy is indicated among symptomatic patients with cholangitis. Patients with choledocholithiasis or biliary stricture may also benefit from endoscopic treatment. Surgical intervention when technically feasible should only be considered in the rare situation when endoscopic interventions are ineffective. |
| **Budd-Chiari Syndrome** |
| 16. Investigation for acquired and inherited thrombotic conditions should be performed in all patients with BCS. Owing to the high prevalence of 2 or more risk factors in BCS, investigation for secondary prothrombotic factors is recommended even in the presence of 1 conspicuous thrombophilia disorder. |
| 17. The hepatic venous outflow tract should be investigated in all patients with acute or chronic liver disease without an obvious cause, particularly in the setting of new-onset ascites and/or abdominal pain. |
| 18. Hepatic venogram and/or liver biopsy are rarely required to make a diagnosis of BCS. |
| 19. Referral to a hematologist is recommended for the evaluation and treatment of specific underlying prothrombotic disorder. |
| 20. Presence of gastroesophageal varices is not a contraindication to anticoagulation. However, primary and secondary prophylaxis for gastroesophageal variceal bleeding should be performed as indicated. |
| 21. Balloon angioplasty of the hepatic vein, with or without stenting, should be reserved for patients with short-segment hepatic vein stenosis. |
| 22. PTFE-covered stents are preferred to bare stents when performing TIPS. |
| 23. Ultrasound-guided DIPS may be attempted when TIPS cannot be accomplished due to complete hepatic vein occlusion. |
| 24. Portosystemic shunt surgeries should be reserved for the rare patients in whom neither TIPS nor DIPS is technically feasible. |
| 25. Patients receiving LT for BCS should be considered for long-term anticoagulation, especially if they have persistent prothrombotic risk, such as myeloproliferative disorders. |
| 26. Prognostic scoring systems are not helpful in guiding choice of therapy. |
| 27. Triphasic contrast-enhanced CT or MRI scans are required for evaluation of hepatic nodules in BCS. |
| **Hereditary hemorrhagic telangiectasia** |
| 28. Standard treatment of LVMs focuses on symptom management of each associated complication including HOHF, PH-related (ascites and variceal hemorrhage), mesenteric ischemia, and bilomas. |

BCS, Budd-Chiari syndrome; CT, computed tomography; DIPS, direct intrahepatic portosystemic shunt; DVT, deep vein thrombosis; HHT, hereditary hemorrhagic telangiectasia; HOHF, high-output heart failure; INR, international normalized ratio; *JAK2*, janus kinase 2; LT, liver transplantation; LVM, liver vascular malformation; MVT, mesenteric venous thrombosis; PC, protein C; PH, portal hypertension; PTFE, polytetrafluoroethylene; PVT, portal vein thrombosis; ROTEM, rotational thromboelastometry; TIPS, transjugular intrahepatic portosystemic shunt; TEG, thromboelastography.

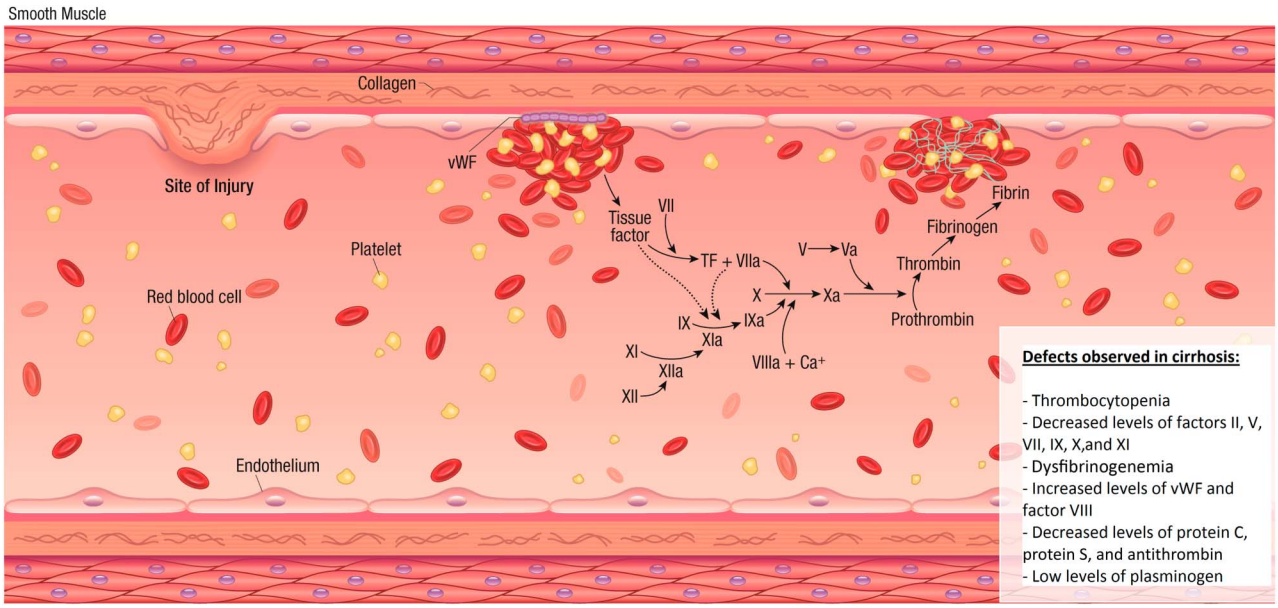


**Figure 2.** Diagram of normal clotting process: vessel injury, platelet plug formation, and clot development and defects observed in cirrhosis.

### Platelets in cirrhosis

As the primary lipid scaffold on which the procoagulant and anticoagulant protease complexes assemble (i.e., the "prothrombinase" complex—XaVa and the "tenase" complex—VIIIaIXa), platelets serve as a fundamental component of thrombin generation and effective hemostasis. Thrombocytopenia results mainly from hypersplenism with platelet sequestration (27), but is also influenced by decreased hepatic synthesis of TPO (an erythropoietin homologue that stimulates marrow megakaryocyte function). Antiplatelet antibodies due to the polyclonal gammopathy of cirrhosis may also contribute to thrombocytopenia. Functional impairment of platelets (thrombocytopathy) has long been suspected in cirrhosis, but elevated endothelial-derived vWF restores platelet function, at least, in part (6,28). Platelet function in cirrhosis is further altered by changes in membrane lipid composition, altered endothelial function, and renal impairment (29,30). Endotoxin-mediated activation of platelets in cirrhosis has also been recently reported (31). Platelet cutoff for bleeding risk is variably reported in mostly retrospective studies (32). *In vitro* studies have indicated adequate human thrombin generation at platelet levels of 50–60,000/uL (33,34).

TPO-receptor agonists (eltrombopag, lusutrombopag, and avatrombopag) have demonstrated to effectively stimulate thrombopoiesis in patients with cirrhosis and thrombocytopenia (35,36). In two large phase 3 randomized trials, the use of avatrombopag at 40–60 mg/d for 5 days significantly reduced the need for platelet transfusions or rescue procedures for bleeding in patients with thrombocytopenia and chronic liver disease undergoing a scheduled procedure (37). Similar results have been observed in a phase 3 placebo-controlled trial of lusutrombopag 3 mg once daily (38). These results led to US Food and Drug Administration approval of avatrombopag and lusutrombopag before elective medical and dental procedures in patients with cirrhosis and platelet count below 50,000/uL. However, TPO-receptor agonists may be associated with an increased risk of thromboembolic events, particularly PVT, in patients with liver disease, and caution is recommended when prescribing these agents (39).

#### *Recommendations*

2. In patients with cirrhosis with platelet count <50,000/mL, is correction of platelet count to >50,000/mL associated with reduced risk of bleeding compared with patients with platelet count <50,000/mL?
   We do not recommend prophylactic platelet transfusions before common procedures such as routine variceal banding or paracentesis outside of significant renal dysfunction (serum creatinine > 2.5 mg/dL) or sepsis. Existing data indicate a somewhat tenuous relationship between bleeding risk and platelet count. *In vitro* studies demonstrate adequate thrombin production with platelet levels ≥50,000/mL. Infusion of a single adult platelet dose does not improve thrombin generation. Higher platelet levels may be more appropriate for high-risk procedures such as removal of large polyps and major surgery, but will probably require higher doses of platelet infusions; if the procedure is elective, the use of TPO agonists may be more appropriate (conditional recommendation, very low level of evidence).

### Bleeding in cirrhosis

Bleeding in cirrhotic patients can be broadly categorized into PH-related bleeding, driven by portal pressure, mucosal/wound bleeding related to hemostatic defects, and AICF (40). AICF is characterized by delayed postprocedure bleeding and mucosal or puncture wound oozing (4,41,42). In contrast to disseminated intravascular coagulation, factor VIII levels are usually high, but fibrinogen levels may decline and, if less than 100, may result in prolongation of PT and PTT. Fibrin/fibrinogen degradation products are usually elevated. Features of hyperfibrinolysis may be detected in up to 30% of hospitalized cirrhotic patients, although clinically evident manifestations are much less frequent (43). When present, however, treatment with antifibrinolytic agents, such as ε-aminocaproic acid or tranexamic acid, can be effective and safe (44).

Portal hypertensive bleeding is not clearly related to laboratory parameters such as platelet count or prothrombin time, and subtle changes in these parameters likely reflect worsening liver disease rather than related hemostatic defects (45,46).

Bleeding following invasive procedures has been variably associated with preprocedure laboratory parameters with the platelet count emerging as the most problematic to interpret (1,47–49). The lack of adequately controlled prospective studies leaves open the question of prophylactic interventions vs rescue strategies should bleeding occur. Viscoelastic testing may be useful to avoid unnecessary blood product use in patients with cirrhosis and severe coagulopathy, but specific parameters are not well established (50,51). Based on studies of thrombin generation in cirrhosis, platelet ranges of 50–60,000/uL are often recommended in high-risk procedures. However, there have been questions about the effects of platelet infusions, and there are further unresolved issues regarding the relative effects of infusion vs use of TPO agonists. In 1 study, a single dose of platelets in patients undergoing variceal band ligation raised the median platelet level from 39,000 to 52,000/uL with no effect on thrombin generation and only mild improvement in ROTEM parameters (34). Notably, no procedure-related bleeding was evident in any of the patients. Extrapolating from studies of bleeding in trauma, and in light of bleeding risk in severely ill cirrhotic patients, fibrinogen levels of >120–150 have also been recommended before high-risk procedures (52). Other strategies to help reduce bleeding risk include control of infection, which is associated with release of endogenous heparinoids, and optimization of renal function, which may affect platelet function and volume (30,53).

***Key concepts***

5. Whole blood viscoelastic tests (thromboelastography and ROTEM) may be useful to avoid unnecessary use of blood products before invasive procedures in patients with cirrhosis and prolonged INR. However, further studies are needed to establish specific parameters for blood product use in this population.

***Recommendations***

3. In patients with cirrhosis and persistent active bleeding, are antifibrinolytic agents effective in reducing bleeding compared with no treatment?
   We do not recommend antifibrinolytic agents such as epsilon aminocaproic acid and tranexamic acid to reduce bleeding in the absence of hyperfibrinolysis. These agents are not generally considered to induce a hypercoagulable state but require caution if pathological clot such as PVT is already present (conditional recommendation, very low level of evidence).

### Hypercoagulability in cirrhosis

Within the liver, activation of hemostatic pathways has been implicated in the pathogenesis of small vessel thrombosis and organ atrophy in a process called parenchymal extinction (54). The potential importance of this process is supported by the results of a long-term prospective trial, wherein therapy with prophylactic doses of low-molecular-weight heparin (LMWH) in cirrhosis without overt thrombotic disease resulted in significantly decreased complications of PH and improved survival (55). PVT and peripheral deep vein thrombosis (DVT) are common problems in patients with cirrhosis (56–58). DVT prophylaxis seems to be safe in hospitalized cirrhotic patients in the absence of both bleeding and platelets less than 50,000/μL (59). The decision to treat active venous thromboembolism in cirrhosis must take into consideration the degree of thrombosis (whether partial or occlusive, and extent), the presence or absence of associated symptoms, relative fall risk, and risk of variceal bleeding. Moreover, monitoring INR is problematic when the patient is on warfarin due to issues surrounding reproducibility in liver disease and uncertain target levels. In the nonacute setting, previous studies of PVT therapy have arbitrarily used INR targets of 2–3 with VKA in extended therapy. This provides at least precedent in the use of these agents in cirrhotic patients with venous thromboembolism, although many issues remain to be resolved. Reduced levels of liver-derived heparin cofactor (antithrombin III) in cirrhosis affect the results of the anti-Xa assay, and whether anti-Xa assay or PTT is better to guide heparin therapy is unresolved (60). Successful use of direct-acting oral anticoagulants (DOACs) such as dabigatran, apixaban, rivaroxaban, and edoxaban has been established in patients with cirrhosis, although these agents are generally avoided in Child-Pugh class B and C patients (61,62). The recent approval of andexanet alfa (reversal agent for Xa inhibitors) means that reversing agents are now available for all the major DOACs.

***Key concepts***

6. Pharmacologic prophylaxis against DVT seems to be safe in hospitalized cirrhotic patients in the absence of bleeding or platelet counts less than 50,000/μL).

## PORTAL AND MESENTERIC VEIN THROMBOSIS IN PATIENTS WITH AND WITHOUT CIRRHOSIS

### Etiology and prevalence

As with any other vascular system, thrombosis of the portal and/or mesenteric veins is related to Virchow's triad including endothelial injury, sluggish blood flow or stasis, and hypercoagulability.

Thrombophilia or increased propensity to thrombosis is the most common cause of PVT in patients without cirrhosis (63–65). The most common inherited causes of thrombophilia in the United States are factor V Leiden mutation and Prothrombin G20210A gene mutation which result in increased activity of the procoagulant factors V and II, respectively. Other inherited causes of reduced anticoagulant activity, including deficiency of antithrombin, PC, or protein S, and antiphospholipid syndrome, are equally prevalent. Myeloproliferative neoplasms are present in about 25% of patients with PVT. Testing for 1849G to 1849T point mutation of the tyrosine kinase janus kinase 2 (*JAK2*) gene in myeloid cells is reported to be very specific and accurate in about 90%–95% of cases in making a diagnosis of myeloproliferative neoplasms (64,66,67). Use of oral contraceptives is another important risk factor for development of PVT (Table 3). Other less common risk factors such as Behçet disease and celiac sprue may also cause PVT but are more often associated with thrombosis of hepatic veins. Furthermore, it must be recognized that there may be more than 1 cause of thrombophilia in a given patient.

The prevalence of PVT in patients with cirrhosis has been reported widely from about 1% in compensated cirrhosis to up to 20% among patients listed for liver transplantation (LT) (68). The prevalence also varies based on the imaging modality used for diagnosing PVT and the length of follow-up (65,69). In 1

**Table 3. Causes of portal or mesenteric vein thrombosis**

| |
|---|
| A. Thrombophilia |
| • Malignancy of any intraabdominal organ |
| • Myeloproliferative neoplasm |
| • Paroxysmal nocturnal hemoglobinuria |
| • Other inherited thrombophilic conditions: PC or protein S deficiency, antiphospholipid syndrome, factor V Leyden deficiency, prothrombin gene mutation, antithrombin deficiency, homocysteinemia, and MTHFR genotype |
| • Pregnancy |
| • Oral contraceptive use |
| B. Local factors with injury to portal or mesenteric veins |
| • Acute intraabdominal process: pancreatitis, ulcerative colitis, Crohn's disease, diverticulitis, cholecystitis, and appendicitis |
| • Intraabdominal surgery: cholecystectomy, colectomy, LT, splenectomy, portosystemic shunting, and TIPS shunt |
| • Abdominal trauma |
| C. Sluggish blood flow |
| • Cirrhosis |
| • Congestive heart failure |

LT, liver transplantation; MTHFR, methyltetrahydrofolate; PC, protein C; TIPS, transjugular intrahepatic portosystemic shunt.

prospective study performed in patients with compensated cirrhosis, a new PVT was discovered in 4.6% and 10.7% of patients at 1 and 5 years of follow-up (65). Patients with cirrhosis may also be at risk of venous thrombosis at other sites (70).

Mesenteric vascular disorders include mesenteric arterial ischemia and mesenteric venous thrombosis (MVT). Mesenteric arterial occlusion is mostly due to cardiovascular and embolic causes and will not be discussed. The risk factors for MVT are the same as described for PVT (Table 3). MVT contributes to about 10%–20% of all mesenteric vascular ischemic disorders, with a prevalence of 1 in 5,000–15,000 inpatient admissions and 1 in 1,000 emergency department admissions (64). Although MVT may occur independently of PVT, more often it results from extension of PVT into the mesenteric veins, given the continuity of the portal vein with the mesenteric veins. Over the past 3 decades or so, the prevalence of MVT has been reportedly rising probably because of increased awareness of the condition and increasing use of cross-sectional imaging in the emergency department among patients presenting with acute abdomen (71,72).

### *Key concepts*

7. Investigation for thrombophilia should be performed for portal and/or mesenteric vein thrombosis among patients without cirrhosis in the absence of obvious etiology such as an acute intraabdominal process. Among patients with cirrhosis, thrombophilia work-up is performed among patients with portal and/or mesenteric vein thrombosis when there is (i) previous history of thrombosis, (ii) thrombosis at unusual sites such as hepatic veins, and (iii) family history of thrombosis.
8. *JAK2* mutation testing should be obtained for evaluation of underlying myeloproliferative neoplasms, the most common thrombophilic etiology for portal and/or mesenteric vein thrombosis in the absence of cirrhosis.

### Clinical features

In patients without cirrhosis, acute thrombosis can involve variable extents of the portal vein and presents with acute abdominal pain, often located in the upper abdomen. Fever is also a common symptom and raises suspicion for an acute intraabdominal process such as diverticulitis, or pyelphlebitis (septic thrombosis of the portal vein), which may be associated with septic shock, bacteremia, and tender hepatomegaly. Other associated features of PVT include abdominal distention from ascites as well as nausea and splenomegaly (73,74). PVT in patients with cirrhosis may also be due to the development of HCC with malignant infiltration into the portal vein. Hence, contrast-enhanced computed tomography (CT) or magnetic resonance (MR) scan adds discerning value to the diagnosis of PVT by enhancing differences of bland and tumor thrombus (75).

PVT may either resolve with complete recanalization especially in patients with cirrhosis or evolve into a chronic thrombus, with development of periportal collaterals (portal cavernoma), PH, and portosystemic collaterals including esophagogastric varices (73). PVT in cirrhotic patients may be associated with worsening PH and/or hepatic decompensation. Whether anticoagulation should be used in cirrhotic patients for prevention of PVT remains controversial. In 1 randomized controlled trial in patients with Child B or C cirrhosis, use of LMWH for 2 years reduced the risk of occurrence of PVT. This benefit of prophylactic anticoagulation in turn resulted in reduced risk of hepatic decompensation and mortality (76).

Both in patients with and without cirrhosis, abdominal pain is the most common presentation of acute MVT. Other common associated symptoms include nausea, vomiting, fever, anorexia, and jaundice (72,73,77,78). The development of fever, abdominal tenderness, ascites, absence of bowel sounds, and laboratory abnormalities such as leukocytosis or increasing lactate levels should raise the suspicion for compromise of intestinal circulation with development of intestinal infarction or gangrene (64,78). Patients with chronic MVT may present with complications of PH, esophageal and/or gastric varices, and variceal hemorrhage.

### Diagnosis

Imaging of the liver and its vasculature is needed to confirm the diagnosis of PVT. Doppler ultrasound (US) may demonstrate hyperechoic material within the vessel lumen, dilatation of the portal vein, and diminished portal venous flow (73,79,80). Ultrasound has a sensitivity of 73%–93%, specificity of 99%, positive predictive value of 86%–97%, and negative predictive value of 98%, when compared with angiogram in 1 study and to CT scan and surgical pathology in another (66,73). Corresponding figures for the accuracy of CT scans to diagnose PVT are 90%, 99%, 99%, and 95%, respectively (73). Advantages of US over CT include lower cost, wider availability, lack of radiation exposure, and being broadly acceptable to patients and physicians (73,79). CT is more accurate in making a diagnosis of PVT extension to mesenteric veins as splanchnic vasculature is not as well visualized on US examination. A central lucency within an expanded and sharply defined vein on contrast, cross-sectional imaging suggests an acute PVT. A tumor thrombus due to HCC is characterized by arterialization of the thrombus. In chronic PVT, often termed cavernomatous transformation of the portal vein, the portal vein is not defined, being replaced by collaterals. The presence of portal cavernoma and features of PH including portosystemic collaterals, splenomegaly, and esophageal varices suggest the diagnosis of chronic PVT. Portal cavernoma usually appears as serpiginous structures in the area of portal vein, with nonvisualization of the main portal vein (81–83). Contrast-enhanced CT scan of the abdomen is approximately 90% accurate in the diagnosis of acute or chronic MVT; accuracy increases with use of multidetector CT scan technique and thin slices of scans (84–86). Associated features of thickened bowel wall and mesentery, indistinct bowel wall margins, and ascites raise suspicion for intestinal infarction or gangrene (86). MRI is an alternative to CT scans to evaluate the mesenteric venous system with advantages of less radiation, better safety profile, and potential for measurement of oxygen desaturation in mesenteric veins in small bowel ischemia (87). MR angiography (MRA) can be performed like CT angiography (CTA); however, this is limited by motion and flow artifacts, longer imaging time, higher cost, signal loss in areas of complex flow, overestimation of stenosis or thrombosis of mesenteric veins, and technical difficulties in patients with implanted metallic devices or surgical clips (88). Many of these limitations can be overcome with 3-D gadolinium-enhanced MRA (89).

#### *Key concepts*

9. Abdominal pain disproportionate to physical findings on abdominal examination should raise suspicion for portal and/or MVT.
10. Among patients with portal and/or MVT, intestinal ischemia is suspected with the development of fever, ascites, rebound abdominal tenderness, leukocytosis, and elevated serum lactate levels.
11. Doppler ultrasound examination of the hepatic vasculature should be obtained in patients with (i) new diagnosis of cirrhosis, (ii) onset of PH, or (iii) hepatic decompensation.
12. Endoscopic evaluation should be performed in patients with chronic PVT to assess for esophageal and/or gastric varices.
13. More data are needed before implementing routine use of prophylactic anticoagulation for prevention of PVT in patients with cirrhosis.

#### *Recommendations*

4. Should Doppler US, CT scan, or MRI be performed for diagnosis of portal and/or mesenteric vein thrombosis?
   We recommend Doppler ultrasound examination as the initial noninvasive modality for diagnosis of PVT. Contrast-enhanced CT or MRI scan is recommended to assess the extension of thrombus into the mesenteric veins and to exclude tumor thrombus among patients with cirrhosis who develop new portal and/or mesenteric vein thrombus (strong recommendation, very low level of evidence).

### Treatment

We discuss management of PVT and MVT in the presence or absence of cirrhosis separately for the following reasons: (i) cirrhosis is an independent risk factor for thrombosis with a higher prevalence of PVT; (ii) cirrhosis impacts both procoagulant and anticoagulant factors; and (iii) differential approach to anticoagulation in the presence of cirrhosis. Management of PVT and MVT revolves around use of anticoagulation and prevention of variceal bleeding. In the absence of hemodynamically significant bleeding, anticoagulation is initiated with infusions of unfractionated heparin or subcutaneous administration of LMWH. Pros and cons of either approach should be considered before starting heparin therapy (Table 4). Initiation of anticoagulation is delayed in patients with active bleeding. Anticoagulation is maintained with oral anticoagulants or LMWH (64). Once again, the pros and cons of either of approach should be considered before choosing the specific regimen (Table 5). Oral directly acting target-specific inhibitors are promising agents, but there is limited experience with these agents.

### Portal or mesenteric vein thrombosis in the absence of cirrhosis

Anticoagulation aims to decrease clot propagation and restore patency of the portal/mesenteric veins. In a prospective study of 102 patients with symptomatic acute PVT in the absence of cirrhosis, 95 patients received anticoagulation. Over a median follow-up period of about 8 months, anticoagulation increased PV patency from 13% to 33% and superior mesenteric vein patency from 42% to 73%, compared with baseline, before initiation of anticoagulation (63).

**Table 4. Advantages and disadvantages of unfractionated heparin infusion and LMWH for initiating anticoagulation**

| | Unfractionated heparin | LMWH |
|---|---|---|
| Administration | Intravenous | Subcutaneous |
| Frequency | Infusion | Twice daily |
| Half-life | Minutes to 1–2 h | 6–12 h |
| Monitoring | Needed with aPTT or Xa | Not needed |
| Renal function | No dose change needed | Contraindicated in renal failure and on dialysis |
| Efficacy | ++ | +++ |
| Heparin-induced thrombocytopenia | +++ | ++ |

aPTT, activated partial thromboplastin time; LMWH, low-molecular-weight heparin.

Anticoagulation is the first-line therapy for patients with symptomatic acute MVT, providing benefits including prevention of bowel ischemia, reduced hospitalization, and improved survival (79,84,90,91). In 1 systematic review of 80 patients with acute MVT in the absence of cirrhosis, 68% received anticoagulation. Mild to moderate self-limited bleeding occurred in 10 cases. Of 50 patients with follow-up imaging available, 50% developed long-term sequela of PH over a median follow-up period of about 2 years; these sequelae were more likely among patients who did not recanalize the thrombosed veins (91). Anticoagulation is given for a finite duration of 3–6 months among patients with reversible etiologies such as acute intra-abdominal process or trauma. Indefinite anticoagulation is required for patients with inherited or acquired thrombophilia (74).

Patients with mesenteric vein thrombosis, who have progressive thrombosis despite anticoagulation and are at risk of intestinal ischemia, may be considered for thrombolytic therapy. In an observational case series including 20 patients with acute mesenteric vein thrombosis who did not improve with anticoagulation, thrombolytic therapy using streptokinase infusion (most commonly through a transhepatic route) was successful in 19 cases with resolution of the thrombus and recanalization of the mesenteric veins (92). The procedure was associated with bleeding in 6 cases; however, none required any major intervention (92). Patients with suspected or confirmed intestinal infarction or gangrene are treated with surgical resection of the compromised bowel. Bowel viability is determined at the time of surgery as the basis for optimizing the extent of bowel resection and prevention of short bowel syndrome (64).

Retrospective studies have demonstrated a lower risk of variceal bleeding in patients with chronic PVT who receive anticoagulation and are maintained on beta-blockers (83,93). The data are scanty comparing band ligation vs beta-blockers for the prevention of variceal bleeding among patients with chronic PVT with varices who require anticoagulation. Based on the randomized data among patients with cirrhosis and esophageal and/or gastric varices, beta-blockers are considered first choice for primary prevention of variceal bleeding and band ligation considered if patients have any contraindication to beta-blockers or do not tolerate these drugs (74).

**Table 5. Advantages and disadvantages of LMWH, VKAs, or DOACs for maintaining anticoagulation**

| | LMWH | VKA | DOAC |
|---|---|---|---|
| Administration | Subcutaneous | Oral | Oral |
| Frequency | Twice daily | Once daily | Once daily |
| Efficacy | Better in malignancy | ++ | ++ |
| Renal function | C/I renal failure | No dose change | No dose change |
| Absorption | Not affected | Affected from bowel edema in PH | Affected from bowel edema in PH |
| Monitoring | Not needed | Needed with PT/INR | Probably not needed |
| Antidote | Available | Available | Available[a] |

[a]Available only in selected centers.
DOAC, direct oral anticoagulants; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; PH, portal hypertension; PT, prothrombin time.

***Recommendations***

5. Should anticoagulation be preferred to thrombolytic therapy as the first strategy in the management of acute portal or mesenteric vein thrombosis?
   We recommend anticoagulation for all noncirrhotic patients with acute symptomatic portal or mesenteric vein thrombosis in the absence of any contraindication (strong recommendation, low level of evidence).
6. Should patients with chronic PVT be treated with anticoagulation or observed?
   We suggest anticoagulation for patients with chronic PVT if there is (i) evidence of inherited or acquired thrombophilia, (ii) progression of thrombus into the mesenteric veins, or (iii) current or previous evidence of bowel ischemia (conditional recommendation, very low level of evidence).
7. In patients with acute symptomatic portal or mesenteric vein thrombosis without a demonstrable thrombophilia, should anticoagulation be administered for 6 months or indefinitely?
   We suggest at least 6 months of anticoagulation in patients with portal or mesenteric vein thrombosis without a demonstrable thrombophilia and when the etiology of the thrombosis is reversible. Indefinite anticoagulation is recommended in patients with portal or mesenteric vein thrombosis and thrombophilia (conditional recommendation, very low level of evidence).
8. Should beta-blockers or endoscopic variceal band ligation be used for primary variceal bleeding prophylaxis in noncirrhotic patients with chronic PVT who require anticoagulation?
   We recommend nonselective beta-blockers for prevention of variceal bleeding in patients with high-risk varices and portal and/or mesenteric vein thrombosis requiring anticoagulation. Endoscopic variceal ligation may be performed if there are contraindications or intolerance to beta-blockers; however, anticoagulation may need to be interrupted in the periprocedural period (strong recommendation, low quality of evidence).
9. Should unfractionated heparin or LMWH be used as the initial agent for anticoagulation among patients with portal and/or MVT?
   We suggest either unfractionated heparin or LMWH be used once a decision is made to initiate anticoagulation for treatment of portal and/or MVT. However, pros and cons of either approach should be considered before initiating either regimen (conditional recommendation, very low level of evidence).
10. Should LMWH or warfarin or direct-acting thrombin or factor Xa inhibitors be used for maintenance of anticoagulation?
    We suggest either LMWH or warfarin be used. Although this field continues to evolve, there is currently only limited experience with DOAC, which includes Xa or thrombin inhibitors. Because absorption of these agents may be limited in the presence of intestinal edema, some monitoring of therapy is recommended. A normal thrombin time and aPTT for dabigatran and a normal prothrombin time or anti-Xa activity for apixaban and rivaroxaban rule out substantial drug effect. Pros and cons of all approaches including availability of reversal agents should be considered before deciding on the specific regimen (conditional recommendation, very low level of evidence).

### Portal or mesenteric vein thrombosis with cirrhosis

There is a general reluctance among practicing physician in considering anticoagulation for patients with cirrhosis. However, in a recent meta-analysis, anticoagulation as compared to no treatment in cirrhotic patients resulted in higher rates of portal vein patency and lower risk of variceal bleeding or worsening of hepatic dysfunction (94). It should be noted that this meta-analysis included only nonrandomized observational studies, and anticoagulation decisions were based on provider's judgment and

were not based on predefined protocols (94). Furthermore, the authors did not perform any subgroup analysis based on the presence or absence of high-risk esophageal varices. Patients with sequela of PH may also be considered for transjugular intrahepatic portosystemic shunt (TIPS), if technically feasible (95). In 1 study, 70 consecutive patients with PVT in the setting of cirrhosis underwent TIPS placement, with recanalization of PV in 57% of patients, particularly those with incomplete PVT or without varices (95). For patients with complete PVT, direct transhepatic or transsplenic approach may be attempted (96,97). It remains unclear whether asymptomatic cirrhotic patients with acute PVT who are not candidates for LT should be treated with anticoagulation, given the conflicting data on survival benefit (65,69,94,98,99). Patients with tumor thrombus from HCC do not derive benefit from anticoagulation (Figure 3), and these patients are best managed as per the current evidence and HCC guidelines (100).

Although PVT among patients listed for LT does not affect waitlist mortality, there is evidence that complete thrombosis of the PV at the time of LT may worsen post-transplant survival (101,102). Limited data on anticoagulation in patients listed for transplant show benefit with complete recanalization of PV in 42% in one and 75% in the other study (103,104). It should be recognized that most patients in both these studies had partial PV thrombosis and only 1 of 19 in the former and 5 of 28 in the latter study had complete thrombosis of the PV (103,104). In cirrhotic patients listed for transplant, anticoagulation should ideally be continued until the time of transplant.

Dependent on center experience and surgical expertise, extensive PVT and/or MVT may lead to removal from the transplant waitlist due to anticipated technical challenges. Multivisceral (liver and small bowel) has been considered for these patients.

### *Key concepts*

14. Anticoagulation among patients with cirrhosis and portal and/or mesenteric vein thrombosis is not associated with increased risk of variceal bleeding.

### *Recommendations*

11. Should anticoagulation be preferred to thrombolytic therapy or no therapy as the first strategy in the management of acute portal or mesenteric vein thrombosis in patients with cirrhosis?
    We recommend anticoagulation for patients with (i) acute complete main PVT, (ii) MVT, or (iii) extension of portal venous thrombosis into mesenteric veins. Risk of bleeding must be weighed against benefits as, e.g, in patients with platelets $<50{,}000/\mu L$ or hepatic encephalopathy at risk of falls (strong recommendation, low level of evidence).
12. Should patients with cirrhosis and chronic PVT be treated with anticoagulation or observed?
    We suggest anticoagulation in patients with chronic PVT only if there is (i) evidence of inherited thrombophilia, (ii) progression of thrombus, or (iii) history of bowel ischemia due to thrombus extension into the mesenteric veins. Anticoagulation may also be considered in patients awaiting LT (conditional recommendation, very low level of evidence).
13. In patients with acute portal or mesenteric vein thrombosis and cirrhosis without an inherited thrombophilia, should anticoagulation be administered for 6 months or continued indefinitely?
    We suggest 6 months of anticoagulation in patients with cirrhosis and acute portal or MVT. Anticoagulation is continued beyond this period in patients with portal or mesenteric vein thrombosis who are on the waiting list for liver transplant (conditional recommendation, very low level of evidence).
14. Should beta-blockers or endoscopic variceal ligation be used for variceal bleeding prophylaxis in patients with cirrhosis and either acute or chronic PVT who require anticoagulation?
    We recommend nonselective beta-blockers for primary prevention of variceal bleeding in cirrhotic patients with high-risk varices and portal and/or mesenteric vein thrombosis requiring anticoagulation. Endoscopic variceal ligation may be performed if there is a contraindication to or intolerance to beta-blockers; however, anticoagulation may need to be interrupted in the periprocedural period (strong recommendation, low quality of evidence).
15. Should unfractionated heparin vs LMWH be used as the initial agent for anticoagulation among patients with cirrhosis and acute portal and/or MVT?
    We suggest either unfractionated heparin or LMWH for treatment of portal and/or MVT once a decision is made to initiate anticoagulation. Unfractionated heparin is preferred in the presence of renal insufficiency, and LMWH is preferred in the presence of thrombocytopenia (conditional recommendation, very low level of evidence).

#### Portal hypertensive or portal cavernoma cholangiopathy

Portosystemic collaterals around the common bile duct in patients with chronic PVT can be associated with common bile duct obstruction. This results in a secondary form of cholangiopathy, termed portal hypertensive cholangiopathy or portal cavernoma cholangiopathy (105). This complication has been reported in about 0.5%–1% of patients with chronic PVT. Patients may present with symptoms of cholestasis including pruritus. These patients are also at risk of developing bacterial cholangitis and intraductal stones (105).

Diagnosis requires presence of a cholestatic liver chemistry profile, portal cavernoma, extrahepatic biliary abnormalities on imaging, and absence of any other etiology to explain the cholangiographic abnormalities (105). MR cholangiogram (MRCP) is used to make the diagnosis. Endoscopic retrograde is required for removal of intraductal stones and/or placement of biliary stents. Portal decompression with a surgical shunt is considered in patients who are refractory to endoscopic intervention (106). Rarely, biliary decompression may require a surgical approach with Roux-en-Y hepaticojejunostomy (106).

### *Key concepts*

15. Endoscopic treatment of portal hypertensive cholangiopathy is indicated among symptomatic patients with cholangitis. Patients with choledocholithiasis or biliary stricture may also benefit from endoscopic treatment. Surgical intervention when technically feasible should only be considered in the rare situation when endoscopic interventions are ineffective.

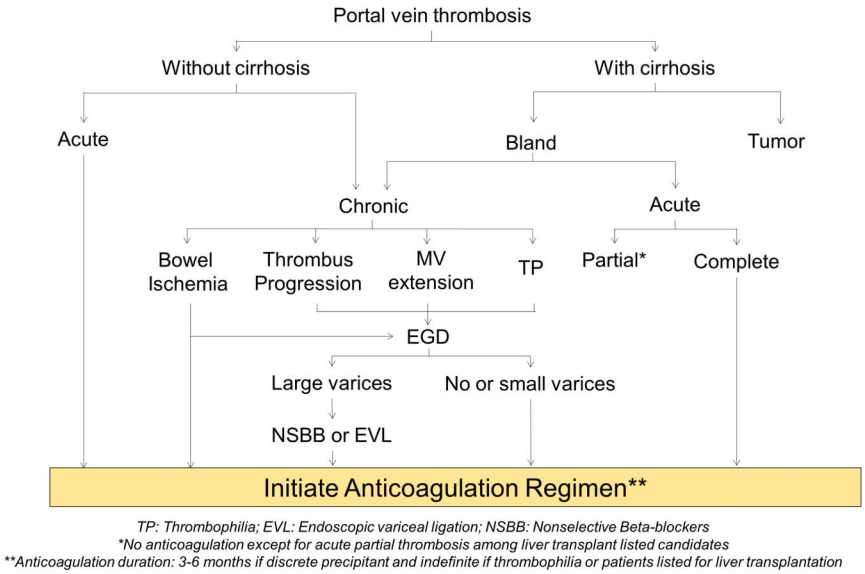


**Figure 3.** Approach to management of portal vein thrombosis.

## BUDD-CHIARI SYNDROME

Primary Budd-Chiari syndrome (BCS) is characterized by thrombotic obstruction of the hepatic venous outflow tract, anywhere from small intrahepatic venules up to major hepatic veins and suprahepatic IVC. Secondary BCS caused by malignant tumors or extrinsic compression of the hepatic veins will not be discussed here. The incidence rate of primary BCS ranges from 0.5 to 2 per million inhabitants in Western countries (107–110), while Asian countries carry the highest prevalence of BCS at 5–7 per million (111,112). The discrepancy between Western and Asian countries may be due to different prothrombotic risk factors (113).

Underlying prothrombotic conditions are identified in most patients with primary BCS. At least 1 thrombotic disorder is present in 79%–84%, while two or more disorders are found in 25%–46% (109,114). Table 6 summarizes the inherited and acquired thrombotic risk factors for BCS. Myeloproliferative disorders (MPN) account for about half of the BCS cases, and are identified through the presence of V617F mutation in the janus tyrosine kinase 2 (*JAK2*) gene in peripheral myeloid cells (115).

### *Key concepts*

16. Investigation for acquired and inherited thrombotic conditions should be performed in all patients with BCS. Owing to the high prevalence of two or more risk factors in BCS, investigation for secondary prothrombotic factors is recommended even in the presence of 1 conspicuous thrombophilia disorder.

### Manifestations and diagnosis

The presentation of BCS ranges from fulminant liver failure to subacute and chronic hepatic venous outflow obstruction, with the latter as the most common presentation. Ascites, abdominal pain, and liver test abnormalities of acute onset are often the initial manifestations of BCS, followed by other complications of PH, including gastroesophageal variceal bleeding and hepatic encephalopathy (114). Approximately 20% of patients are asymptomatic, and the diagnosis is made incidentally (116). Although laboratory investigation often reveals abnormal liver biochemistry, the diagnosis of BCS relies on imaging studies. Occlusion of hepatic veins and/or IVC, caudate lobe hypertrophy, patchy enhancement of hepatic parenchyma, and intrahepatic or extrahepatic venous collaterals are radiographic features of BCS (117,118). A prospective study of 173 consecutive patients with BCS comparing the performance characteristics of Doppler US, CT, and MRI scan, demonstrated high agreement rates between the 3 modalities (117). In addition, Doppler ultrasonography is noninvasive, low cost, and correlates well with pathology and venogram findings (119–121). At present, hepatic venogram and liver biopsy are rarely needed for solely diagnostic purposes. Focal nodular hyperplasia, adenomas and HCCs may be seen on imaging studies.

### *Key concepts*

17. The hepatic venous outflow tract should be investigated in all patients with acute or chronic liver disease without an obvious cause, particularly in the setting of new-onset ascites and/or abdominal pain.
18. Hepatic venogram and/or liver biopsy are rarely required to make a diagnosis of BCS.

### *Recommendations*

16. Should Doppler US, contrast-enhanced CT scan, or MRI be obtained to diagnose BCS in patients with new-onset ascites?
    We recommend Doppler US as the initial diagnostic test for evaluation for BCS. Contrast-enhanced CT or MRI scans should be obtained to assess thrombus extension, rule out tumor thrombus, determine response to anticoagulation therapy, evaluate indeterminate hepatic nodules, and whenever there is high clinical suspicion of BCS despite negative or inconclusive Doppler US results (conditional recommendation, low level of evidence).

**Table 6. Prothrombotic risk factors for BCS**

| |
|---|
| A. Acquired thrombophilia |
| • Myeloproliferative disease |
| • Polycythemia vera |
| • Essential thrombocytosis |
| • Idiopathic myelofibrosis |
| • *JAK2* V617F mutation |
| • Paroxysmal nocturnal hemoglobinuria |
| • Behçet disease |
| • Hyperhomocysteinemia |
| • Antiphospholipid syndrome |
| B. Inherited thrombophilia |
| • Factor V Leiden |
| • Prothrombin gene G20210A mutation |
| • MTHFR C677T mutation |
| • Thalassemia |
| • PC deficiency |
| • Protein S deficiency |
| • Antithrombin deficiency |
| C. Systemic factors |
| • Sarcoidosis |
| • Vasculitis |
| • Behçet disease |
| • Connective tissue disease |
| • Inflammatory bowel disease |
| D. Hormonal factors |
| • Recent oral contraceptive use |
| • Pregnancy |

BCS, Budd-Chiari syndrome; *JAK2*, janus kinase 2; MTHFR, methyltetrahydrofolate; PC, protein C.

## Management

The management of BCS encompasses medical therapy with anticoagulation, vascular interventional radiological procedures, including angioplasty and TIPS, decompressive portosystemic shunt surgery, and LT. Unfortunately, randomized clinical trials comparing treatment modalities in BCS are lacking. Such studies are difficult to complete, given the rare nature of this condition and variable presentation at different stages. Thus, an individualized multidisciplinary stepwise approach is recommended.

## Medical therapy

Targeted therapies of the underlying prothrombotic disorders are indicated; however, these options are only currently available for MPN and paroxysmal nocturnal hemoglobinuria. Cytoreductive therapies, such as hydroxyurea, pegylated-interferon, busulfan, and ruxolitinib (122), may be used in MPN, while eculizumab, an anticomplement agent, may be considered in paroxysmal nocturnal hemoglobinuria (123,124). Referral to a hematology specialist to determine whether patients may benefit from such agents is strongly recommended.

Systemic anticoagulation is the first-line treatment of BCS, independent of the demonstration of thrombotic risk factors. Warfarin has been used for long-term anticoagulation, while unfractionated heparin and LMWH are often used in the acute setting. DOACs have not yet been investigated in BCS, although data on patients with splanchnic vein thrombosis and cirrhosis have been promising (125). Major bleeding is unfortunately common in patients with BCS on anticoagulation, with an overall incidence of up to 22.8 episodes per 100 patient-years (126). Invasive procedures and portal hypertension are responsible for majority of bleeding.

### *Key concepts*

19. Referral to a hematologist is recommended for the evaluation and treatment of specific underlying prothrombotic disorder.
20. Presence of gastroesophageal varices is not a contraindication to anticoagulation. However, primary and secondary prophylaxis for gastroesophageal variceal bleeding should be performed as indicated.

## Interventional vascular therapies

The goal of endovascular interventions is to decompress the hepatic sinusoids by restoring adequate hepatic venous outflow. Thrombolysis, balloon angioplasty and/or stenting aim to achieve recanalization of obstructed vessels, while TIPS entails the creation of an intrahepatic shunt as a means of decompressing the hepatic sinusoids. Systemic or arterially delivered thrombolytic agents, such as recombinant tissue-type or urokinase-type plasminogen activator, are ineffective in BCS. Local infusion of these agents into the hepatic vein and/or IVC can potentially be effective in reestablishing vascular patency when combined with balloon angioplasty (127). The low success rate of thrombolysis can be explained by the chronicity of most cases of BCS at presentation (128). Thrombolytic agents may still have a role when there is acute occlusion of hepatic vein stents or TIPS (127). Hepatic vein angioplasty, with or without stenting, has been found particularly beneficial in a small subset of BCS patients with short-segment hepatic vein stenosis (129). However, long-term success with angioplasty, even in combination with anticoagulation, is limited to about a third of patients (130,131).

TIPS is a less-invasive method of portal decompression than surgical shunts with excellent long-term outcomes, thus reducing the need for surgical shunts and LT in BCS (132,133). In a large prospective multicenter European study including 157 patients with BCS, 39.5% of patients underwent TIPS, and of these, only 6.45% required a liver transplant, while only 2% underwent surgical shunting (130). In another study, 60% of patients failed medical therapy and underwent rescue TIPS, achieving good long-term results (134). In this series, however, the majority of patients (60%) developed late TIPS dysfunction and required TIPS revision. The routine use of polytetrafluoroethylene (PTFE)-covered stents has significantly reduced the incidence of TIPS dysfunction and the need for additional interventional procedures. Compared with bare stents, the dysfunction rate has decreased from 87% to 30%–40% or less with PTFE-covered stents (135,136). In the small subset of patients in whom TIPS may not be technically feasible due to complete hepatic vein obstruction, ultrasound-guided direct intrahepatic portosystemic shunt (DIPS) connecting the portal vein and IVC may be an acceptable alternative (137,138).

A large systematic review and meta-analysis of 29 retrospective observational studies on 2,255 patients with BCS treated with endovascular interventional therapies analyzed the outcomes of recanalization procedures (thrombolysis, balloon angioplasty, and/or stenting) and TIPS. Recanalization procedures carried a success rate of 93.1% with a 5-year survival of 88.6%, while TIPS was associated with 96.4% success rate and 5-year survival of 72.1% (139). Given significant heterogeneity among the studies and presumed selection bias toward sicker patients in the TIPS group, comparisons between recanalization procedures and TIPS may not be meaningful.

***Key concepts***

21. Balloon angioplasty of the hepatic vein, with or without stenting, should be reserved for patients with short-segment hepatic vein stenosis.
22. PTFE-covered stents are preferred to bare stents when performing TIPS.
23. Ultrasound-guided DIPS may be attempted when TIPS cannot be accomplished due to complete hepatic vein occlusion.

### Surgical management

Long-term survival has been reported in 1 series to be as high as 95% with side-to-side portocaval surgical shunts for medically refractory BCS (140); however, portosystemic shunting surgeries have been historically associated with significant perioperative mortality (10%–20%), particularly in patients with advanced liver disease (141,142).Therefore, surgical shunting has fallen out of favor in the past 2 decades, and it has been largely replaced by less-invasive approaches, such as TIPS (114).

***Key concepts***

24. Portosystemic shunt surgeries should be reserved for the rare patients in whom neither TIPS nor DIPS is technically feasible.

### Liver transplantation

Approximately 10%–15% of patients with BCS may require LT during the course of their disease because of failure of medical and/or endovascular interventions (114). Reported 5-year patient survival after transplant has improved in the recent decades, ranging from 70% to 92% (130,143–147). Recurrent thrombosis after transplant has been reported in as many as 20% of patients, and long-term anticoagulation should be considered in all patients because of persistent prothrombotic risk after transplant (146). Many inherited hypercoagulable conditions, however, may be reversed as LT can correct conditions such as factor V Leiden mutation, prothrombin gene mutation, protein S and C deficiencies, and antithrombin deficiency.

Except in the rare patient presenting with fulminant liver failure, a stepwise approach in the management of BCS has been widely adopted (131). A large, prospective, multicenter European study on 157 patients, with a median follow-up of 5 years, demonstrated an overall survival of 77% with this approach (130). In this study, 88.5% of patients received long-term anticoagulation, and 44% did not require any invasive interventions. Angioplasty and/or thrombolysis were pursued as initial treatment in 14% of patients, of which 64% required escalation of care to either TIPS or liver transplant. Approximately 40% of patients underwent TIPS, and of those, only 6.35% went on to require a liver transplant. The 5-year transplant-free survival of patients with BCS treated with TIPS is between 72% and 78% (130,132).

Several prognostic indices have been developed to help predict outcomes in BCS over the years (132,142,148,149). The Rotterdam score is one of the most studied prognostic tools in BCS, and it has been validated to predict intervention-free survival in BCS (130). However, the ability to accurately predict transplant-free survival remains unsatisfactory (150). Furthermore, prospective validation is needed to determine whether the use of prognostic scores to guide therapy improves survival, and thus, scores should not be used to dictate treatment in individual patients (150).

***Key concepts***

25. Patients receiving LT for BCS should be considered for long-term anticoagulation, especially if they have persistent prothrombotic risk, such as MPN.
26. Prognostic scoring systems are not helpful in guiding choice of therapy.

***Recommendations***

17. Should anticoagulation or interventional radiology treatment with angioplasty or TIPS be the initial treatment of choice for patients with BCS?
    We recommend stepwise management from least to most invasive therapies for patients with BCS. Systemic anticoagulation is the initial treatment of choice. If medical therapy fails, as determined by worsening liver and/or renal function, ascites, or hepatic encephalopathy, then endovascular therapies such as angioplasty or TIPS are recommended. LT is reserved for TIPS failure and BCS presenting as fulminant liver failure (strong recommendation, moderate level of evidence).

### Risk of HCC

Benign regenerative hepatic nodules are frequently observed in BCS and may be difficult to distinguish from HCC by imaging criteria alone (151). Approximately a third of benign lesions in BCS demonstrate washout on portal and/or delayed phases, significantly reducing the specificity of this finding for HCC diagnosis (152). A small longitudinal study, with 5-year follow-up, demonstrated an increase in the number and size of benign nodules in BCS over time (153). Approximately 25% of these nodules may represent hepatic adenomas, although they carry a distinct immunohistochemical phenotype compared with conventional adenomas (154). This may suggest different tumor behavior and potentially a higher risk of malignant transformation. A systematic review including 16 studies from distinct geographic regions demonstrated a pooled prevalence of HCC of 15.4% in patients with BCS (95% confidence interval: 6.8%–26.7%), excluding those with concomitant viral hepatitis (155). Of note, significant heterogeneity was observed among the studies, which included 12 studies from Asia, 2 from Africa, and only 1 from Europe and North America. The European study by Moucari et al. (156), including 97 patients with BCS with median follow-up of 5 years, demonstrated a cumulative HCC incidence of 4%. This study also found that alpha-fetoprotein level may help distinguish benign nodules from HCC with 100% positive predictive value and 91% negative predictive value for a cutoff level of 15 ng/mL.

***Key concepts***

27. Triphasic contrast-enhanced CT or MRI scans are required for evaluation of hepatic nodules in BCS.

***Recommendations***

18. Should patients with chronic BCS undergo HCC surveillance vs no surveillance?
    We suggest surveillance for HCC with abdominal ultrasound and serum alpha-fetoprotein levels every 6 months in patients with chronic BCS. Diagnosis of HCC is challenging, and patients are best referred to centers of expertise for diagnosis (conditional recommendation, low level of evidence).

## MESENTERIC ARTERY ANEURYSMS

The splanchnic circulation includes the celiac, superior mesenteric, and inferior mesenteric arteries, all arising from the abdominal aorta. Mesenteric arterial aneurysms are seen in 10% of autopsies, but infrequently cause problems. The aneurysms may be complicated by rupture and the mortality rate after rupture is as high as 70%. Little is known about the natural history and clinical presentation of mesenteric artery aneurysms.

A true aneurysm is a permanent, localized dilatation (>1.5 times the expected diameter) of an artery and involves all 3 layers of the vessel wall. A pseudoaneurysm ("false aneurysm") is a localized disruption of the intimal and medial layers of the artery. Pseudoaneurysms are lined by adventitia or perivascular tissue and are caused by trauma. Fusiform aneurysms involve the entire circumference, and saccular aneurysms involve only a portion of the vessel wall. Patients with mesenteric artery aneurysms usually present after the sixth decade of life. Splenic artery aneurysms account for about 60% of all mesenteric artery aneurysms and are more common in multiparous women. Hepatic artery aneurysms are the next most common aneurysms. A male preponderance is noted for hepatic and gastroduodenal artery aneurysms. Both sexes are affected equally with celiac and superior mesenteric artery aneurysms. Aneurysms are multiple in approximately one-third of patients. Because the aneurysms are small, they are not usually palpable, although a bruit may be heard (157). CTA is performed to characterize mesenteric artery aneurysms and inform management decisions. Most splanchnic artery aneurysms are asymptomatic and detected incidentally on imaging studies. The factors associated with rupture are uncertain. Therefore, the uncertainty behind management decisions needs thorough discussion with the patient. It is generally recognized that pseudoaneurysms have a higher risk of rupture than true aneurysms. Although the risk of rupture of splenic artery aneurysms in pregnancy may be low, when rupture does occur, there is a high risk of maternal and fetal mortality. That is the reason behind recommending treatment for splenic artery aneurysms in women of childbearing age. Typical symptoms associated with mesenteric artery aneurysms include abdominal pain and intraabdominal and GI bleeding. Patients with acute pancreatitis are at increased risk of developing pseudoaneurysms due to local enzymatic vascular injury, with associated mortality rates between 30% and 50% when aneurysms rupture (158).

### Management

Mesenteric artery aneurysms associated with symptoms (abdominal pain in the absence of other causes) and pseudoaneurysms associated with acute pancreatitis should be treated irrespective of diameter or location. Intervention is considered for aneurysms greater than 2–2.5 cm in diameter even if asymptomatic (159). In patients with mesenteric aneurysms smaller than 2–2.5 cm in diameter, follow-up imaging is recommended initially in 6 months, then at 1 year and subsequently every 1–2 years. In patients with true asymptomatic mesenteric aneurysms, intervention irrespective of diameter may be considered for aneurysms of the pancreaticoduodenal and gastroduodenal arcade; intra-parenchymal hepatic artery branches; in women of childbearing age; and liver transplant recipients. Although open repair with arterial reconstruction has been recommended for aneurysms of the proper hepatic artery, excellent results are obtained using endovascular stents with lower morbidity. Coil embolization may be considered for aneurysms not involving proper hepatic artery. In general, a minimally invasive approach to management is preferred (160). Follow-up CTA imaging is considered at 3-yearly intervals after endovascular repair. No follow-up imaging is recommended for pseudoaneurysms treated by embolization.

For patients with portal vein aneurysm, intervention is recommended only in the presence of thrombosis or symptoms. In patients without liver disease, portal vein aneurysm repair is recommended, while in patients with PH, portosystemic shunt procedures may be considered. LT is also a corrective procedure for portal vein aneurysms.

***Recommendations***

19. Should asymptomatic mesenteric artery aneurysms <2 cm in diameter be observed or treated?
    We suggest treatment in asymptomatic patients only with aneurysms of the pancreaticoduodenal and gastroduodenal arcade, intraparenchymal hepatic artery branches, women of childbearing age, and recipients of a liver transplant, irrespective of aneurysm diameter. In asymptomatic patients with mesenteric aneurysms <2 cm in diameter and not meeting the aforesaid criteria, follow-up imaging is recommended initially in 6 months, then at 1 year and subsequently every 1–2 years. We recommend that mesenteric artery aneurysms associated with symptoms (abdominal pain in the absence of other causes) be treated (conditional recommendation, low level of evidence).
20. Should asymptomatic mesenteric artery aneurysms >2 cm in diameter be observed or treated?
    We recommend intervention for all aneurysms >2 cm in diameter even when asymptomatic (strong recommendation, low level of evidence).

## HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary hemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu disease, is a genetic disorder with autosomal dominant inheritance, characterized by widespread cutaneous, mucosal and visceral telangiectases that affects 1 in 5,000–8,000 people in the general population (161). The pathogenesis of HHT in at least 80% of the patients is related to heterozygous mutation in 1 of two genes, endoglin and activin receptor-like kinase type 1 (ALK-1 or ACVRL1), that encode transmembrane proteins involved in the transforming growth factor beta family of receptors that are mostly expressed in the vascular endothelium (162). Mutations in another gene, SMAD4, lead to a combined syndrome of HHT and juvenile polyposis (162).

The liver is included among the viscera involved in HHT, and symptomatic liver involvement is more common in HHT-2, the type associated with activin receptor-like kinase type 1 mutations. Based on results from 3 large recent cohorts, liver vascular malformations (LVMs) on imaging are present in 55% of patients with definite HHT (163–165).

Given the dual blood supply to the liver (hepatic artery and portal vein), there are 3 types of shunting that can occur with these LVMs, and each of them may result in a different clinical presentation (162).

1. Hepatic artery to hepatic vein shunting (the most common) results in high-output heart failure (HOHF) and/or in ischemic cholangiopathy with secondary sclerosing cholangitis and/or biloma formation;
2. Hepatic artery to portal vein shunting results in PH;
3. Portal vein to hepatic vein shunting may lead to portosystemic encephalopathy (PSE) and could also contribute to HOHF.

Since not all these communications are "arterio"-venous a more appropriate term for them is "LVMs." The 3 types of shunting likely occur concomitantly, but usually one of them predominates functionally and clinically.

The 3 most common types of clinical presentations associated with LVM are (166):

1. HOHF is the most common (63%) of the complications and is secondary to arteriovenous and/or, less often, portovenous shunting leading to a hyperdynamic circulatory state. It is manifested by dyspnea on exertion, orthopnea, peripheral edema, and ascites and can be complicated by atrial fibrillation, pulmonary hypertension, and tricuspid regurgitation.
2. Biliary ischemia (19% of cases) due to arterioportal shunting (blood supply to bile ducts is exclusively from hepatic artery) that can lead to biliary necrosis, biloma formation that can become infected, and secondary sclerosing cholangitis. Biliary ischemia manifests as pain in the right upper quadrant, occasionally with fever, jaundice, and/or pruritus with a cholestatic liver panel.
3. PH (17% of cases) due to arterioportal shunting but mostly from nodular regenerative hyperplasia (NRH) that results from irregular vascular blood supply (any of the 3 types of shunting) and results in a nodular configuration of the liver that had been misinterpreted as "cirrhosis" in the past. NRH may be characterized by ascites, variceal hemorrhage, and splenomegaly. NRH may lead to elevated serum alkaline phosphatase, but, in general, liver synthetic function is normal.

Other less common presentations are as follows:

4. Hepatic encephalopathy which can result from intrahepatic portohepatic vascular malformations or from extrahepatic portosystemic collaterals secondary to PH, akin those that occur in cirrhosis.
5. Mesenteric ischemia (abdominal pain after meals) that results from hepatic artery steal, i.e., blood is shunted through the enlarged and high-flow hepatic artery and away from the mesenteric artery.

Although children with HHT have been found to have LVMs on imaging, symptomatic LVMs only occur in adults with a mean age of around 48 years at presentation (163–165); the youngest individual with reported symptomatic LVMs is 21 years old (164).

A minority (8%–14%) of patients with definite HHT and LVM are symptomatic at diagnosis of HHT (164,165). In the largest natural history of patients with HHT and LVMs, ~3.5% per year of asymptomatic patients developed overt symptoms, and 5% had died in a median follow-up of 44 months with a median age at death of 75 years (164).

Except for PH, other presentations occur predominantly in women. Although unusual, pregnancy in women with HHT and LVMs can trigger severe heart failure and/or biliary ischemia that may lead to a "hepatic disintegration syndrome" (167).

Importantly, symptoms can transition from one presentation to another (e.g. predominant HOHF to biliary ischemia). The different symptomatic presentations can be precipitated by anemia (from GI bleed/epistaxis) and can occur concurrently or sequentially (e.g., heart failure that then transitions to biliary ischemia) (168,169).

***Recommendations***

21. Is screening for LVMs in patients with HHT associated with better outcomes?
    We do not recommend routine screening for LVMs in patients with HHT. There is no evidence to suggest that making a diagnosis in an asymptomatic patient has clinical benefits or prevents death. However, those with a liver bruit, hyperdynamic circulation, or liver test abnormalities should be further evaluated for LVMs. Of note, women with HHT and LVMs who become pregnant warrant special attention due to anticipated hemodynamic stress (strong recommendation, low level of evidence).

**Diagnosis**

The presence of LVMs can be suspected clinically (even in asymptomatic patients) by finding an audible bruit and/or palpable thrill over the hepatic region and/or by finding abnormal liver tests (typically elevated alkaline phosphatase, with occasionally elevated bilirubin and/or aminotransferases).

The definitive way to establish the diagnosis of LVMs is through imaging studies: The hallmark findings are intrahepatic hypervascularization (or telangiectases) and an enlarged common hepatic artery (>6–7 mm), abnormalities that have been demonstrated by angiography previously (angiography is not currently recommended), Doppler ultrasonography (170,171), spiral and multidetector CT (172,173), and MRI (174). These abnormalities are more obvious in the symptomatic patient. The most used methods to demonstrate vascular malformations are CTA or MRA, and there seems to be no difference regarding their diagnostic accuracy (175).

The type of shunting can be determined in more than two-thirds of the patients with LVMs by the detection of early or differential enhancement of hepatic veins (arteriovenous shunting) or portal veins (arterioportal shunting) during various phases of imaging. Although arterioportal shunting is found significantly more frequently in patients presenting with PH, there is no correlation between CT and clinical presentation (173). In addition, portovenous shunts are difficult to diagnose on standard noninvasive imaging studies. Focal lesions compatible with focal nodular hyperplasia are more commonly seen in patients with HHT (prevalence of 2.9%) compared with the general population (prevalence 0.3%); similarly, and as described previously, NRH is a frequent finding leading to an erroneous

diagnosis of cirrhosis. There are no reports of HCC arising from the nodules of a liver with LVMs in HHT.

Liver biopsy is not indicated in patients suspected to have LVMs, not only because the procedure may be associated with an increased risk of bleeding, given the presence of widespread LVMs (176), but also because histology is not helpful in making the diagnosis and the combination of regeneration (NRH) and fibrosis (accompanying ectatic vessels) can lead to a misdiagnosis of cirrhosis.

### *Recommendations*

22. Should Doppler US or CT/MRI scan be performed for diagnosis of LVMs in patients with HHT and symptoms suggestive of LVMs? We suggest contrast CT scan or MRI/MRCP in patients with HHT who develop symptoms/signs of heart failure, biliary ischemia, hepatic encephalopathy, mesenteric ischemia, or PH. Doppler US may establish a diagnosis of LVMs in patients with HHT and a compatible clinical picture, but is less accurate than CT scan or MRI/MRCP. Angiography and/or liver biopsy are not recommended in the diagnosis of LVMs (strong recommendation, low level of evidence).

### Standard therapy

No treatment is recommended for asymptomatic LVMs. Treatment for symptomatic LVMs depends on the specific presentation and is associated with a high rate of complete response (162).

HOHF responds initially to treatment with sodium restriction, diuretics, and beta-blockers. In addition, treatment should be focused on the correction of anemia and atrial fibrillation which can exacerbate symptoms by decreasing oxygen delivery and compromising cardiac output, respectively. Pregnant patients who develop HOHF should be treated medically and delivered as expeditiously as possible. PH treatment is focused at the specific related complications (ascites, varices, and variceal hemorrhage) as recommended for patients with cirrhosis. Notably, placement of a TIPS does not ameliorate bleeding from GI arterio-venous malformations (177). In patients with evidence of secondary sclerosing cholangitis, ursodeoxycholic acid may be used, although there are no data to support this contention. Bilomas require no treatment as long as they are asymptomatic; if they are associated with abdominal pain, analgesics are initially recommended. Patients with evidence of infection (either cholangitis or infected biloma) should receive antibiotics urgently. Biloma drainage should be considered if pain or infection is not improving. In patients with mesenteric ischemia, initial treatment should consist on smaller and more frequent meals and analgesics.

### Targeted therapy

For patients unresponsive to standard therapy, treatments targeted at the pathophysiological mechanisms should be considered. The least invasive consists of infusions of bevacizumab, followed by embolization or ligation of the hepatic artery and then LT. Unfortunately, the evidence for these therapies is based on case reports or case series with only a couple of prospective studies including small cohorts of patients with LVMs and mixed clinical presentations. One of the main problems with most of the publications is an insufficient description of the standard therapy used and its intensity before considering transition to the targeted therapy.

***Bevacizumab.*** It is an antibody that neutralizes vascular endothelial growth factor and acts as an antiangiogenic drug (178). In patients with HOHF, a prospective cohort study of 24 patients underwent echocardiography before and 3 months after a course of bevacizumab, showed normalization of cardiac index in 3 (12%), improvement but not normalization in 17 (71%), and a lack of response in 4 (17%) cases (179). A concomitant improvement in epistaxis could have contributed to this amelioration. Unfortunately, predictors of response were not analyzed. Bevacizumab in this study was administered at a dose of 5 mg/kg of body weight by intravenous infusion every 14 days for a total of 6 doses. In a retrospective cohort study of patients on bevacizumab that most probably included patients from the previous cohort but with a longer follow-up, mortality was 42% in a subset of 26 patients with LVMs (2 died within 6 months of last bevacizumab dose; 2 between 6 and 12 months and 7 between 1 and 4.4 years). In addition, 3 patients required orthotopic liver transplantation (180).

In a case series of 3 patients with ischemic cholangiopathy, bevacizumab was administered at the same dose was followed by a maintenance infusion (every 3 months for 12 months). The study demonstrated resolution of symptoms and amelioration of imaging abnormalities in all patients, although one of them developed sepsis while on bevacizumab (6 months); 2 patients who had been considered for LT were no longer candidates (181). Follow-up after discontinuation of bevacizumab was not described. This is important because another retrospective study including 21 patients with HOHF and/or abdominal angina showed that clinical symptoms recur gradually at varying intervals between 5 and 26 months requiring repeat dosing, and 14% were nonresponders and required more invasive therapy (182).

Side effects more commonly reported with bevacizumab are arthralgias, headache, proteinuria, arterial hypertension, and poor wound healing (180,183), which have raised concerns about complications after LT in patients who proceed to orthotopic liver transplantation while on the drug.

***Hepatic artery occlusion.*** It (embolization or surgical ligation) is pathophysiologically rational in alleviating HOHF and mesenteric angina where high flow from the hepatic artery to the hepatic vein is the main mechanism of disease. Although initial amelioration or resolution of symptoms has been reported, the effect is mostly transient, and treatment is associated with significant morbidity and mortality, mostly related to biliary and/or hepatic necrosis leading to death or need for urgent LT in up to 30% of the cases (162). It follows that hepatic artery occlusion should be proscribed in patients with biliary disease.

Also, in the largest series of patients subjected to particle/coil embolization, 6/20 (30%) patients died in a mean follow-up of 33 months with 4 of the deaths occurring in patients with PH/portosystemic encephalopathy presentation (184). Therefore, hepatic artery occlusion should also be proscribed in patients with PH.

Surgical banding/ligation of the common hepatic artery and 1 branch of the left or/and right hepatic artery was evaluated in 35 patients with liver VMs (185). Twenty-two patients were excluded because they were either asymptomatic, had biliary disease, significant portovenous shunting with hepatic encephalopathy, impaired liver function, or "irreversible" cardiopulmonary changes. There were 13 patients treated (mean age of 42 years) with shortness of breath, many of whom also had abdominal pain, and 6 had PH. In this unusual cohort, improvement in shortness of breath and abdominal angina were reported, while 2 patients developed postoperative biliary ischemia that was reversible. In a mean follow-up of 50 months, there was only 1 death from cerebral hemorrhage (185).

***Liver transplantation.*** LT has been examined in the largest series (n = 40) of patients with HHT and liver VMs from the European

Liver Transplant registry (186). Most patients had HOHF (14 patients) or severe biliary ischemia/hepatic necrosis (12 patients, at least 5 resulting from hepatic artery embolization). Indications for LT were not specified, although 25 patients were being regularly hospitalized or in hospital at time of LT. Cardiovascular function, determined by echocardiography and/or right heart catheterization in 24 patients, showed improvement after LT in 75% and stabilization in the rest; 1 patient died of acute heart failure at day 2 after LT. The actuarial 1-, 5-, and 10-year patient and graft survival rates were excellent at 82.5%. However, early complications (within 4 months) occur in 55%–60% of the patients (186,187), and in the large cohort, 7 (17.5%) patients died during or very early after LT (186). In addition, there is now clear evidence of recurrence of liver VMs in the graft occurring as early as 6 years after LT. In a long-term follow-up study of 14 transplanted patients with HHT and LVMs, recurrence (detected by abnormal radiological features and/or liver biopsy) occurred in 8 (57%) patients in a mean follow-up of 127 months (range 74–184 months) after transplant (188). The estimated cumulative risk of recurrence was 48% at 15 years. Interestingly, liver tissue analysis showed microchimerism with presence of vascular lining cells of recipient origin. Further follow-up is expected to determine whether recurrent LVMs become symptomatic.

### *Key concepts*

28. Standard treatment of LVMs focuses on symptom management of each associated complication including HOHF, PH-related (ascites and variceal hemorrhage), mesenteric ischemia, and bilomas.

### *Recommendations*

23. In patients with HHT and symptomatic LVMs, is bevacizumab more effective in resolving symptoms and/or avoiding invasive therapies (HA embolization/transplant) than standard therapies?
We recommend standard medical therapy for each complication of liver VMs in patients with HHT, which results in symptom resolution in the majority. In nonresponders to standard therapy, management should be undertaken at specialized centers using a multidisciplinary approach. Bevacizumab should be considered in patients with HOHF and possibly for other complications of LVM before using invasive therapies, although not all patients respond. Symptoms recur after treatment discontinuation, and bevacizumab can be associated with significant side effects. Transarterial hepatic artery embolization or surgical ligation is proscribed in patients with biliary involvement or PH, and there is insufficient evidence to recommend its use in HOHF. Liver transplant is an important option for nonresponders to standard treatment or patients who relapse after medical treatment, but criteria for listing are not clearly defined, the procedure may be associated with a high rate of perioperative complications, and liver VMs may recur as early as 6 years after transplant (conditional recommendation, low level of evidence).

## ACKNOWLEDGMENTS

This guideline was produced in collaboration with the Practice Parameters Committee of the American College of Gastroenterology. The committee gives special thanks to Bennie Upchurch, MD, FACG, who served as guideline monitor for this document. The authors thank Patricia J. Erwin, Mayo Clinic College of Medicine and Science, for help with references.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Patrick S. Kamath, MD.

**Specific author contributions:** All authors were involved in drafting and editing the manuscript. All authors approved the final draft submitted.

**Financial support:** No funding was received for this publication.

**Potential competing interests:** None to report.

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