Clinical Monograph

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Guidance for Coagulation Management in Patients With Acute or Chronic Liver Failure

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Abstract: This monograph delineates clinical guidance for the diagnosis and management of patients with liver disease who have coagulation disorders or who are at risk for thromboembolic events, including approaches to anticoagulation in patients with liver disease who have a history or are at future risk for thromboembolism through acquired or inherited hypercoagulability. The monograph also discusses care of patients before and after liver transplant in reference to coagulation disorders. This guidance focuses on the evaluation and management of coagulopathy in patients with chronic liver disease, as well. Given the paucity of evidence-based data in this area, this monograph is based on both a detailed review of the literature combined with expert opinion. The clinical circumstances for each individual patient must be considered and integrated into the management plan on a case-by-case basis.

GASTROENTEROLOGY & HEPATOLOGY

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Background and Evaluation of Hypercoagulability

Robert G. Gish, MD, and Fredric G. Regenstein, MD

The Clotting Process

Abnormalities of laboratory hemostatic parameters, as well as clinical disorders related to bleeding and thrombosis, are common in patients with liver disease, especially those with cirrhosis or acute liver failure. The endothelial proteins von Willebrand factor (VWF) and thrombomodulin among others can also be used to define the status of clotting in patients with cirrhosis. The normal clotting process begins with spontaneous or iatrogenic tissue injury, including to the vascular endothelium, leading to the initiation and formation of the platelet plug. This platelet plug formation is specifically initiated by damage to the endothelium. This damage can also result from other types of physical trauma to the vessel, chronic overexposure to stress hormones or inflammatory mediators, or physical rupture of plaque, as in coronary artery disease. Endothelial damage exposes platelets to collagen, which in turn promotes platelet adherence and activation. Activated platelets secrete both adenosine diphosphate and thromboxane A2, which are synthesized via the arachidonic acid pathway. Adenosine diphosphate and thromboxane A2 both promote further platelet recruitment and aggregation, resulting in the formation of a platelet plug.

The clotting process is then propagated by the coagulation cascade and controlled and also terminated by antithrombotic control mechanisms. Endothelial damage exposes blood to subendothelial tissue factor, which is found in the extravascular tissues. Intravascular sources of tissue factor, including endothelial cells and monocytes, have also been identified. Tissue factor is also found on hepatocytes, but is usually hidden from the circulation
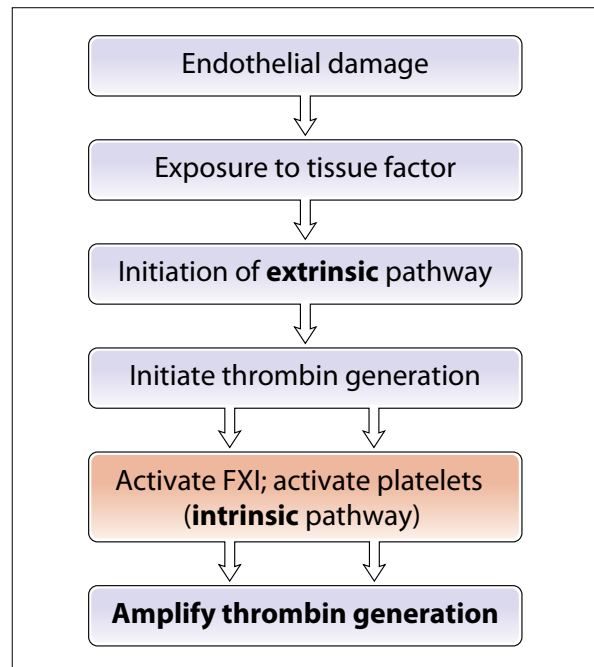

Figure 1. Endothelial damage: initiation of thrombin generation. FXI, factor XI.

(encrypted). Injury can cause de-encryption. The reason this is important is that intrasinusoidal coagulation is activated in liver injury, leading to microvascular thrombosis and a possible "second hit" in the presence of local ischemia. Sources of intravascular tissue factor (eg, endothelial cells, blood cells) are normally repressed; however, during an inflammatory state, such as sepsis, intravascular tissue factor production may increase. Exposure to tissue factor initiates activation of the extrinsic or tissue factor path-

way, which in turn initiates thrombin generation. After the initial generation of a small amount of thrombin, the tissue factor pathway is rapidly inhibited by the activation of tissue factor pathway inhibitor. However, the thrombin that is generated is able to activate platelets to build more platelet surface through aggregation and to produce a surface that is conducive to procoagulant activity through the expression of phospholipids. In addition, the initial amount of thrombin activates factor XI in the intrinsic pathway. Activation of factor XI, along with the creation of a platelet procoagulant surface, amplifies the generation of thrombin via the intrinsic "tenase" and prothrombinase complexes (Figure 1).

Thrombin generation is the pivotal point of the coagulation process. The prothrombotic actions of thrombin include amplification of thrombin generation via factor XI and platelet activation, as well as clot formation via conversion of fibrinogen to fibrin and the activation of factor XIII, which is required for the crosslinking of fibrin. The interaction of platelets and thrombin generation results in the formation of the fibrin-platelet clot, a barrier that impedes blood loss. Ultimately, the clot may be removed by fibrinolysis.

Clotting in Patients With Liver Disease

Among patients with liver disease, the clotting process is impacted by several events. Chief among them is a deficiency in the synthesis of the factors necessary for the coagulation cascade. All coagulation factors (except VWF, factor VIII [partially synthesized in the liver], and calcium) are produced in the liver. Factors II, VII, IX, and X are dependent on vitamin K; thus, factor deficiency can be related to vitamin K deficiency, decreased synthetic function, or increased consumption. In patients with liver disease, decreased levels of vitamin K are common for 2 reasons: dietary deficiency and lack of absorption in those with cirrhosis. In addition, in cirrhosis or acute liver failure, there is a lack of functional interaction with vitamin K in the liver cell. Furthermore, on the procoagulant side, there is also decreased degradation of activated coagulation factors, decreased synthesis of anticoagulant factors such as protein S and protein C, as well as synthesis of abnormal coagulation factors (including abnormal fibrinogen). Table 1 lists other clotting alterations noted in patients with cirrhosis.

Interestingly, cirrhosis predisposes patients to venous thrombosis and potentially to venous thromboembolism. These clotting events, especially when they occur in the portosystemic circulation, are a serious clinical problem. Commonly encountered clinical scenarios include portal vein thrombosis, Budd-Chiari syndrome, deep venous thrombosis and pulmonary embolism, thrombotic

Table 1. Clotting Alterations in Patients With Cirrhosis

Abnormality	Description
Platelet abnormalities	Decreased amount • Splenic sequestration • Decreased thrombopoietin levels • Bone marrow suppression • Autoantibody destruction Increased function (minor) • New platelets: old platelets are selectively destroyed/sequestered in the spleen Poor function • Uremia • Changes to vessel wall phospholipid composition
Hyperfibrinolysis	Accelerated intravascular coagulation and fibrinolysis • Resembles disseminated intravascular coagulation, except for markedly elevated factor VIII • Parallels degree of liver dysfunction • Mild systemic fibrinolysis is found in 30% to 45% of cirrhotic patients. Clinically evident fibrinolysis is seen in 5% to 10% of patients • Ascites is associated with increased fibrinolytic activity

diathesis leading to nodular regenerative hyperplasia, progression of cirrhosis with parenchymal extinction nodules, and hepatic artery and portal vein thrombosis after liver transplant.

Separately, acquired or inherited thrombophilias can manifest in the portal or hepatic veins and result in thrombotic liver disease. Such patients may require thoughtful anticoagulation management to treat blood clots, as well as thromboprophylaxis before and after procedures. The evaluation of acquired and inherited thrombophilia in patients with venous or arterial thrombosis and liver disease is important because these disorders impact the success of liver transplant and the patient's prognosis.[1] Identification of a specific prothrombotic state may guide subsequent therapy, influence duration of therapeutic anticoagulation, and increase precautionary measures in the care of these patients.

Based on the patient's clinical scenario, history, findings, signs, and symptoms, it may be necessary to test for the acquired or inherited thrombophilias listed in Table 2. A personal or family history of thromboembolic events is an important part of the evaluation, and may be present in patients without an identifiable inherited clotting disorder. A negative test evaluation does not preclude an unidentified inherited disorder. Screening for protein C,

Table 2. Acquired or Inherited Thrombophilias

Disorder	Testing—NOT Perturbed by Abnormal Hemostatic Parameters or Anticoagulation	Testing—Perturbed by Abnormal Hemostatic Parameters or Anticoagulation
Factor V Leiden	Genetic testing	APC-resistance test
Prothrombin gene mutation	Genetic testing	
Protein C deficiency		Protein C activity (low)
Protein S deficiency		Protein S activity (low)
ATIII deficiency		ATIII activity (low in liver disease and with heparin; can be elevated with warfarin)
Familial FVIII elevation		FVIII activity (elevated in liver disease and inflammation)
Hyperhomocysteinemia and homocystinuria (cystathionine beta synthase deficiency)	Serum homocysteine massively elevated (>100 µmol/L; often 200-400 µmol/L). Part of newborn screen in many states	
Acquired Disorders		
Antiphospholipid syndrome	Anti-cardiolipin antibodies, anti–β2-GPI-antibodies	DRVVT for lupus anticoagulant
Myeloproliferative neoplasm	*JAK2* mutation (V617F and exon 12-15); *CALR, MPL* mutations	
Paroxysmal nocturnal hemoglobinuria	Flow cytometry of peripheral blood or bone marrow for CD59 and CD55	
Protein S deficiency in HIV-positive patients		

APC, activated protein C; ATIII, antithrombin III; DRVVT, dilute Russell viper venom time; FVIII, factor VIII; GPI, glycosylphosphatidylinositol.

protein S, and antithrombin deficiencies in liver failure by direct blood levels is often futile or confusing because levels are often low due to the liver disease. Conversely, factor V Leiden and factor II gene tests are never false-positive.

Portal vein thrombosis is the most common macro-thrombotic manifestation in patients with liver disease, occurring in 8% to 18% of patients with cirrhosis.[2,3] The risk for portal vein thrombosis is lower in patients with Child-Pugh A disease, increases with worsening liver dysfunction and decreased portal flow, and is increased in patients with liver disease due to nonalcoholic steatohepatitis who are undergoing liver transplant.[4-7] Deep venous thrombosis and pulmonary embolism are other forms of macrothrombotic complications, which have been reported in 5% of hospitalized patients with acute and chronic liver disease.[8]

Microthrombotic complications include intrahepatic microthrombi ("parenchymal extinction") resulting in nodules,[9] portopulmonary hypertension, and cirrhosis as an ischemic/reinjury process.

Coagulopathy of Liver Disease

The coagulopathy of liver disease refers to the prolonged plasma coagulation (measured as prolonged prothrombin time [PT]), coupled with low blood platelet counts, that is observed in patients with cirrhosis.[3,10] The understanding of coagulopathy in patients with liver disease has greatly evolved over the past 2 decades.[11]

Originally, it was thought that patients with advanced liver disease with prolonged clotting times had "auto-anticoagulation." However, more recent data have contradicted this theory, and have recognized an increased prevalence of thrombotic complications in patients with liver disease and cirrhosis. Thus, there is no "auto-anti-coagulation" in cirrhosis, and instead there is a concept of "rebalanced hemostasis." This terminology reflects a careful balance in which the hemostatic imbalance caused by a decrease in the hepatic synthesis of procoagulants is "rebalanced" by a concomitant decrease in the hepatic synthesis of anticoagulant proteins (Table 3).[12]

However, major events such as gastrointestinal bleeding, infection, and renal failure can upset the delicately rebalanced hemostasis of cirrhosis.

Evaluation for Hypercoagulability

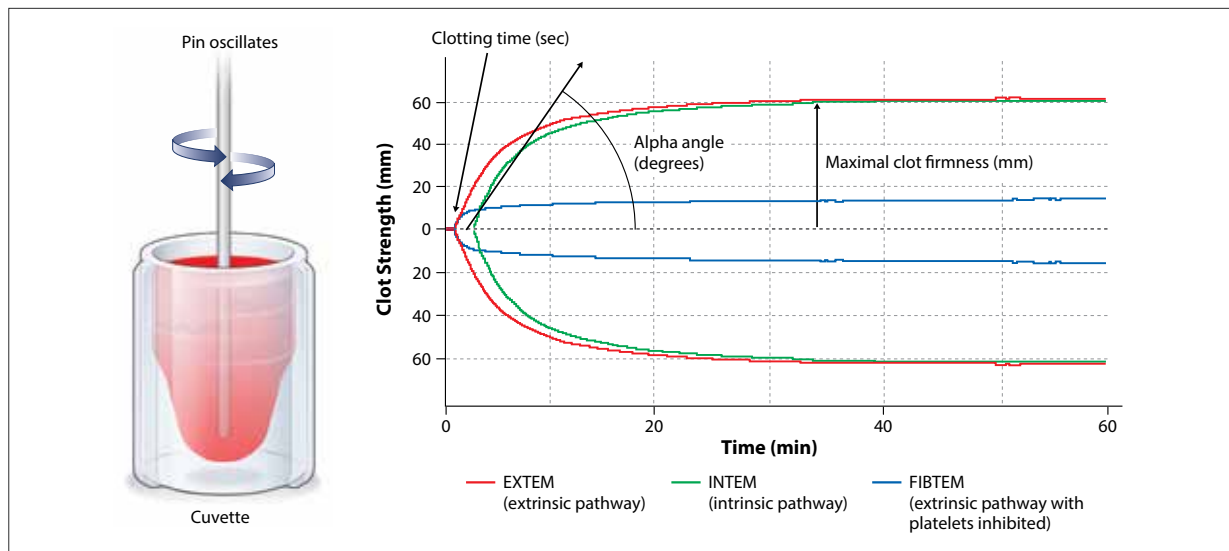Evaluation for hypercoagulability (Table 4) should be considered in appropriate patients, especially those with

Figure 2. Rotational thromboelastometry: clot formation in whole blood. Courtesy: R. Todd Stravitz, MD.
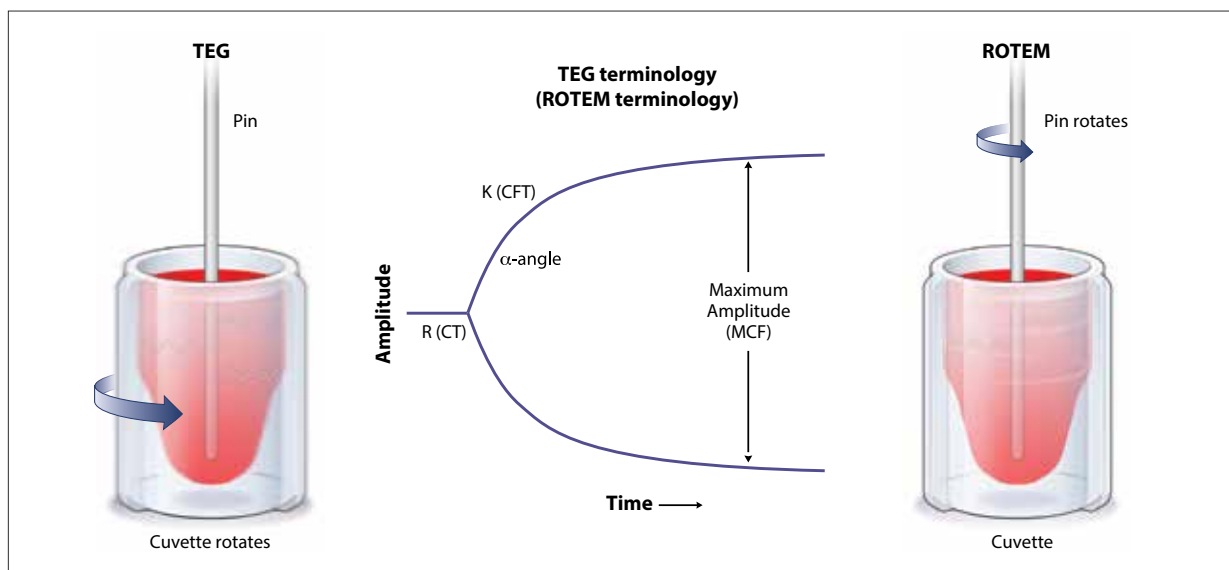

Figure 3. Viscoelastic measurement of clot formation in whole blood. ROTEM, rotational thromboelastometry; TEG, thromboelastography. Courtesy: R. Todd Stravitz, MD.

family history, unprovoked/unexplained venous or arterial thromboembolism, and venous thromboembolism in an unusual location (ie, splanchnic or hepatic vein thrombosis, dural venous sinus thrombosis).

Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM)

The PT test was originally designed for the management of patients receiving warfarin and is the foundation for evaluating blood clotting and dysfunction in vitamin K–dependent coagulation factors among patients tak-

ing warfarin. This measurement is now expressed as an international normalized ratio (INR) and used broadly in assessing patients' coagulation status in many clinical settings. PT and the INR reflect some of the coagulopathy associated with synthetic dysfunction in patients with end-stage liver disease. INR has been validated as a prognostic marker for liver disease mortality (as a component of the Model for End-Stage Liver Disease [MELD] score),[13] but not for bleeding risk. There can be wide interlaboratory variation in INR among patients with liver disease due to many confounding factors.[14] Importantly, routine diagnostic tests, such as the PT/INR and the platelet count,

Figure 4. The parameters of a temogram using the terminology for TEG. R, measure of coagulation time from start to initial fibrin formation. Alpha angle, the angle between the midline and a line tangential to the developing "body" of the TEG trace. Represents clot kinetics of clot buildup and crosslinking. MA, maximum amplitude is the maximum width of the "body" of the TEG trace. Represents ultimate clot strength.
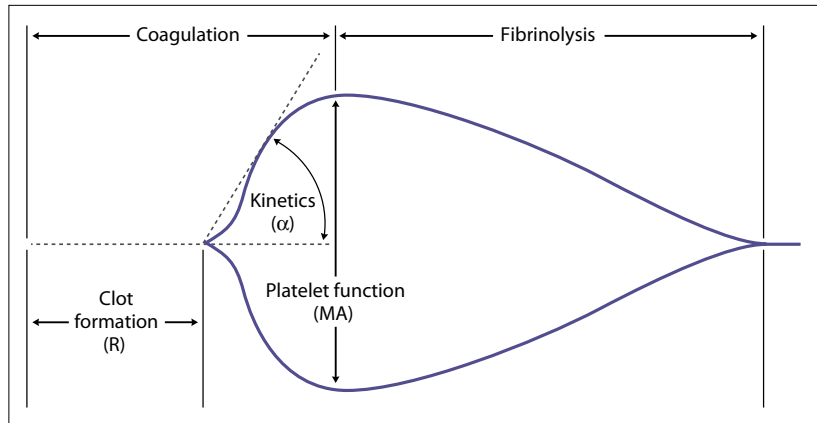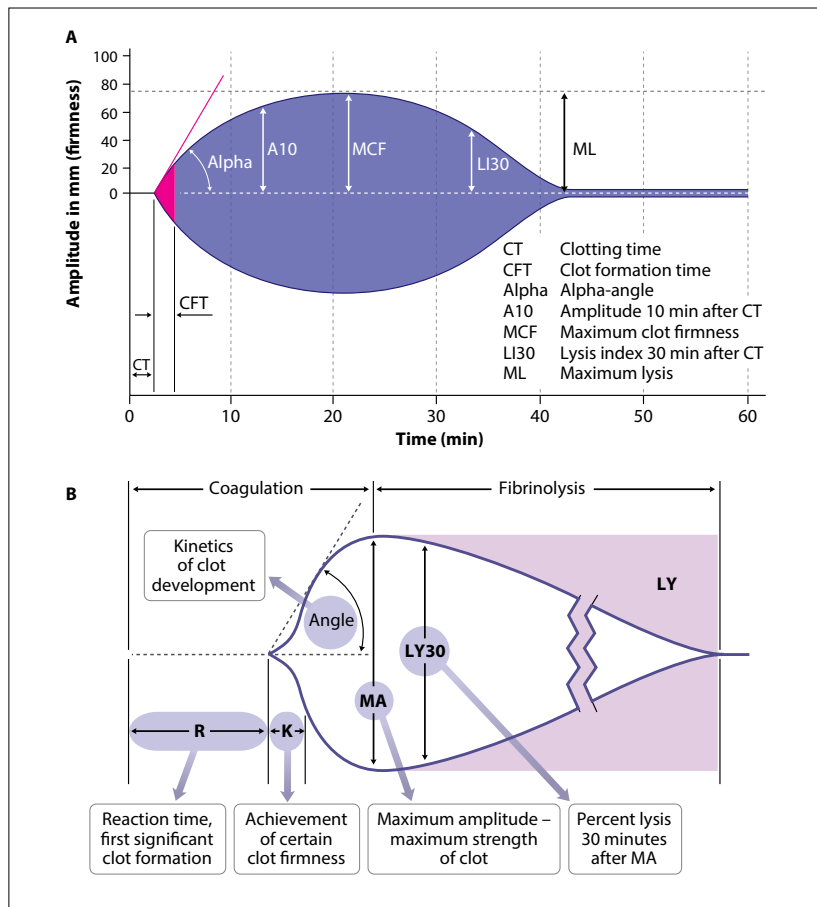

Figure 5. A comparison of the terminology used in ROTEM (A) and TEG (B). The depictions demonstrate clot initiation, propagation, stabilization, and lysis. Adapted from Whiting D and DiNardo JA. *Am J Hematol.* 2014;89(2):228-232.[18]

do not adequately reflect the hemostatic status in patients with liver disease.

Bleeding episodes frequently occur in patients with liver disease and may be related to dysregulated hemostasis. However, bleeding episodes cannot be predicted by routine diagnostic tests, such as the PT/INR. Poor synthetic liver function and vascular endothelial dysfunction result in altered plasma levels of coagulation proteins, anticoagulation proteins, and factors involved in fibrinolysis, which confound bleeding risk assessment. Thus, an evaluation based on the INR or activated partial thromboplastic time (aPTT) is sensitive only to the levels of coagulation proteins and therefore not suitable to determine the overall hemostatic balance that helps define bleeding or thrombotic risk in patients with liver disease. aPTT has little use in the evaluation of patients with acute and chronic liver disease. Likewise, the level of predisposition to bleeding in liver disease due to thrombocytopenia—frequently caused by splenic pooling and/or reduced production of thrombopoietin—remains unclear.

Table 3. The Concept of "Rebalanced Hemostasis" in Chronic Liver Disease

Changes That Impair Hemostasis	Changes That Promote Hemostasis
Thrombocytopenia	↑ Levels of von Willebrand factor
Impaired platelet function	↓ Levels of ADAMTS-13
↑ Production of nitric oxide and prostacyclin	↑ Level of factor VIII
↓ Levels of factors II, V, VII, IX, X, XI	↓ Levels of protein C, protein S, antithrombin, α2-macroglobulin, and heparin cofactor II
Vitamin K deficiency	↓ Levels of plasminogen
Dysfibrinogenemia	
↓ α2-antiplasmin, factor XIII, and TAFI	
↑ t-PA levels	

ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TAFI, thrombin-activatable fibrinolysis inhibitor; t-PA, tissue plasminogen activator.

Table 4. Evaluation for Hypercoagulability

Tier 1 Can be useful in clinical circumstances (special caution with recent thrombotic event or use of anticoagulation)	• Factor V Leiden mutation • Prothrombin gene mutation • Antithrombin activity • Protein C level, activity • Protein S level, activity • Lupus anticoagulant assay (eg, DRVVT, PTT-LA) • Antiphospholipid (β2 glycoprotein, cardiolipin) antibodies, IgG, and IgM
Tier 2 Useful in certain circumstances; order in consultation with hematologist	• Factor VIII level (cirrhotic patients have elevated levels, confounding interpretation) • *JAK2* V617F mutation testing with reflex to exon 12-15, *CALR, MPL* (consider with Budd-Chiari syndrome, polycythemia, normal platelet count despite portal hypertension, splenomegaly out of proportion to degree of cirrhosis) • PNH flow cytometry for CD59 and CD55 (very rare; consider with pancytopenia, hemoglobinuria, iron deficiency)

DRVVT, dilute Russell viper venom time; Ig, immunoglobulin; PNH, paroxysmal nocturnal hemoglobinuria; PTT-LA, partial thromboplastin time–lupus anticoagulant.

Instead, thromboelastography (TEG) and a similar technique termed rotational thromboelastometry (ROTEM) are considered the most accurate tests to evaluate hypercoagulable, hypocoagulable, and rebalanced coagulation status and to help guide selection of anticoagulation therapy and indicate whether anticoagulation is even needed. The TEG and ROTEM analyzers measure both the kinetic and physical properties of clot formation. The kinetic properties include the time to initial fibrin formation and the rate of fibrin-clot buildup. The physical properties include clot quality or strength, which is dependent on platelet function, and clot stability, which is dependent on the extent of clot lysis. Table 5 provides a comparison of standard hemostatic laboratory tests with TEG/ROTEM parameters among healthy individuals and those with varying degrees of liver injury.[15,16]

A standard TEG/ROTEM records 5 parameters.[15] The variables measured by TEG and ROTEM are shown in Table 6.[17] The reaction (r)-time (in minutes) shows the time of clot latency from the beginning of the clotting reaction to the initial formation of fibrin. The r-time loosely corresponds to INR and aPTT. The kinetic (k)-time (in minutes) is defined as the time required for the initial fibrin formation to reach a specific clot firmness. The α-angle (in degrees) represents the kinetics of clot formation and reflects the rate of fibrin formation and crosslinking. The maximum amplitude (MA, in mm) corresponds to the maximum clot strength and is also primarily dependent on the platelet count and function of platelets and the concentration of fibrinogen. Clot lysis at 30 minutes (Lysis-30; in percent) shows the clot dissolution within 30 minutes of reaching maximum amplitude, corresponding to fibrinolysis. ROTEM is shown in Figure 2. Viscoelastic measurement of clot formation in whole blood is shown in Figure 3. Figure 4 illustrates the parameters of a temogram using the terminology for TEG. Figure 5 provides a comparison of the terminology used in TEG and ROTEM.[18]

Increasing evidence suggests that the net effect of a decrease in procoagulant and anticoagulant clotting factors in liver disease provides a relative rebalance of hemostasis. Prolonged PT (INR) and aPTT only crudely reflect the procoagulant pathway and are therefore not predictive of bleeding or thrombosis. In addition, the thrombocytopenia of liver disease does not reliably predict the risk of periprocedural or spontaneous bleeding events. This may be the case partly because liver disease platelets pooled by the spleen are systemically available, and may function well due to increased levels of VWF. We suggest that, instead of using PT and aPTT to assess coagulation status among patients with cirrhosis, those medical centers with TEG devices available should begin using TEG/ROTEM, complemented by measurement of fibrinogen levels and platelet count.

Table 5. Comparison of Standard Hemostatic Laboratory Tests and TEG/ROTEM Parameters in Healthy Individuals and in Patients With Liver Disease

Parameter	Normal Range	ALI/ALF (N=51)	Cirrhosis (N=273)	Cirrhosis INR ≥1.5 (N=48)
Standard hemostatic laboratory tests				
INR	0.9-1.1	3.4±1.7	1.3±0.3[c]	1.7±0.4[c]
Fibrinogen (mg/dL)	200-450	195±84	263±108[b]	179±89
Platelets (× 10⁹/L)	172-440	186±95	112±79[c]	84±46[c]
TEG parameters[d]				
Reaction time (min)	2.5-7.5	4.7±1.9	4.4±1.2	4.2±1.5
Kinetic time (min)	0.8-2.8	1.7 [0.8-20.0]	2.2 [0.8-16.6]	2.8 [1.2-16.6][b]
α-angle (degrees)	55.2-78.4	63.7±12.2	62.6±9.3	58.1±10.8[a]
Maximum amplitude (mm)	50.6-69.4	55.0±10.9	51.5±10.4[a]	45.0±9.9[d]
Lysis-30 (%)	0.0-7.5	0.0 [0.0-2.1]	0.5 [0.0-5.2][d]	0.25 [0.0-3.2][a]

ALF, acute liver failure; ALI, acute liver injury; INR, international normalized ratio; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

Patients with cirrhosis and an INR of 1.5 or greater were selected from the overall cirrhosis cohort. Normal range is for the local laboratory. Values are given as mean±standard deviation or median [range].

[a]$P<.05$. [b]$P<.001$. [c]$P<.0001$. All comparisons are vs ALI/ALF. [d]TEG was performed on a Thrombelastograph Haemostasis Analyzer 5000 (Haemonetics Corp., Haemoscope Division). Clotting was initiated at 37°C by the addition of kaolin to 0.34 mL of recalcified blood.

Adapted from Stravitz RT. *Gastroenterol Hepatol (N Y)*. 2012;8(8):513-520[15] and Hugenholtz GCG et al. *Res Pract Thromb Haemost.* 2017;1(2):275-285.[16]

Table 6. Variables Measured by TEG and ROTEM

Variable	TEG	ROTEM
Measurement period	-	Reaction time
Time from start to when waveform reaches 2 mm above baseline	R	Clotting time
The time from 2 mm above baseline to 20 mm above baseline	K	Clot formation time
Alpha angle [°]	Slope between R and K	Angle of tangent at 2 mm amplitude
Maximum angle	-	CRF
Maximum strength	Maximal amplitude	Maximal clot firmness
Time to maximum strength	-	Maximal clot firmness–t
Amplitude at a specific time	A30, A60	A5, A10
Clot elasticity	G	Maximum clot elasticity
Maximum lysis	-	CLF
Clot lysis at a specific time (minutes)	CL30, CL60	LY30, LY45, LY60
Time to lysis	2 mm from maximal amplitude	CLT (10% difference from maximal clot firmness)

CLF, maximum lysis; CLT, clot lysis time; CRF, clot formation rate; K, clot kinetics, measuring time taken for a certain level of clot strength to be reached; R, measure of coagulation time from start to initial fibrin formation; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

Adapted from Thromboelastography [TEG] & Rotational Thromboelastometry [ROTEM]. Practical-Haemostasis.com. https://www.practical-haemostasis.com/Miscellaneous/Global%20Assays/teg_rotem.html. Updated January 5, 2021. Accessed January 12, 2021.[17]

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Anticoagulation in Patients With Chronic Liver Disease

Robert G. Gish, MD, and Steven L. Flamm, MD

Patients With Cirrhosis and Underlying Synthetic Dysfunction

Most patients with chronic liver disease do not manifest clotting disorders until they develop cirrhosis. At this point, patients usually exhibit subtle clinical signs of liver failure, evident as synthetic dysfunction that manifests in several ways. The first 2 signs are a reduction in the serum albumin level, which reflects the reduced capacity of the liver to synthesize albumin, and increased direct bilirubin. Another major event, which occurs later in the course of the disease in most patients, is prolongation of the prothrombin time (PT)/international normalized ratio (INR). All coagulation factors are synthesized by the liver (with the notable exceptions of factor VWF:VIII and Ca++), and thus PT/INR can be crudely used to measure the liver's synthetic ability. Once cirrhosis with synthetic dysfunction is evident, a full evaluation for bleeding and clotting risk is needed (including thromboelastography [TEG]/rotational thromboelastometry [ROTEM]). This coagulation assessment with TEG/ROTEM is of critical importance in patients with acute liver failure.

Therapeutics

The effectiveness of anticoagulation with enoxaparin, a low-molecular-weight heparin (LMWH), in preventing portal vein thrombosis in patients with advanced cirrhosis was demonstrated in a randomized, controlled trial.[1] In this study, 70 Italian outpatients with cirrhosis were ran-

Table 1. Target INR for Therapeutic Anticoagulation With Warfarin

Target INR	Indication
2.0-3.0	Atrial fibrillation Initial deep venous thrombosis Pulmonary embolism Occasionally bioprosthetic valves
2.5-3.5	Mechanical heart valves
1.8-2.2	Baseline abnormal INR and presence of varices or other portal hypertension signs, portal hypertensive gastropathy, and/or gastric arterial vascular ectasia

INR, international normalized ratio.

domly assigned to receive prophylactic enoxaparin or no treatment for 48 weeks. The results are shown in Figure 1. By 48 weeks, 6 of the 36 patients (16.6%) in the control group had developed a portal vein thrombosis, compared with no patients in the enoxaparin group (P=.025). This benefit was extended to 96 weeks, at which time, none of the enoxaparin group had developed a portal vein thrombosis, compared with 10 of 36 patients (27.7%) in the control group (P=.001). During the follow-up period, off therapy, 3 enoxaparin-treated patients developed a portal vein thrombosis, at weeks 105, 111, and 121 after enrollment. Further, liver decompensation occurred more commonly in patients in the control group compared with patients treated with enoxaparin (59.4% vs 11.7%; P<.0001). Kaplan-Meier estimates showed a higher rate of survival in the enoxaparin-treated group compared with the control group (P=.020). Since patients receiving treatment with enoxaparin decompensated less than the controls, this study also suggests that enoxaparin prevents microvascular thrombosis and slows parenchymal extinction, suggesting that Dr Ian Wanless was right all along.[2]

Initiating Anticoagulation Therapy

Anticoagulation therapy must be individualized, based on each patient's liver function status, the presence of portal hypertension, previous bleeding events, current risk of bleeding, plans for invasive procedures, and risk for falls. Prior to the initiation of anticoagulation therapy, the patient's primary care physician should be contacted to discuss indications for therapy and identify which office will be primarily responsible for long-term anticoagulation management. In many cases, this requires a physician-to-physician conversation, as only one office should be responsible for anticoagulation management of the patient. Additionally, the indication for anticoagulation and the goal INR therapeutic range (Table 1) should be notated in the medical record. For patients who are

clinically stable and who do not have advanced renal disease or a history of heparin-induced thrombocytopenia, warfarin can usually be safely initiated in the outpatient setting with bridging therapeutic-dose LMWH. The risk of accumulation of the anticoagulant effect has led to the suggestion that patients with a creatinine clearance of 30 mL/min or less (≤0.50 mL/s) should be excluded from treatment with LMWH or should undergo anti–factor Xa heparin level monitoring.[3] For titration of warfarin, the reader should follow his or her institution's protocols.

Dietary Guidelines for Patients on Warfarin

Patients should not markedly change their diet from the one they were on when warfarin was started. Key to this is the intake of vitamin K: because the warfarin dose is calculated based on the patient's vitamin K level, it should remain consistent from day to day. In its reduced form (vitamin K_1 dihydroquinone, vitamin K hydroquinone), vitamin K is an essential cofactor for post-translational activation of vitamin K–dependent clotting factors (the procoagulant factors II, VII, IX, and X, and the anticoagulant proteins C and S).[4] It is notable that this advice differs from older guidelines, which recommended that patients on warfarin restrict their diets to limit intake of vitamin K. In addition to foods high in vitamin K, patients should avoid greatly increasing or decreasing the intake of drugs and foods listed in Table 2.

Suggested Measures for Management of INR Changes With Warfarin

The following principles may guide the clinician when managing INR changes with warfarin:
- Check INR prior to first dose; additionally, check daily during titration or with medication changes that affect INR levels.
- Do not administer more than 1 warfarin dose per day, with preferential administration in the evening.
- Changes in INR might not be seen until 3 to 4 days after initiating or adjusting the warfarin dose.
- The lower end of the acceptable INR range should be targeted for patients with the following characteristics: elderly (>65 years old), recent surgery or a recent (<3 months) history of gastrointestinal bleed, poor nutritional status, potential for drug interactions, or decompensated cirrhosis.
- If warfarin is stopped, INR levels require up to 4 to 5 days to normalize (to approximately 1.0 in non–liver disease patients from an INR of 2.0-3.0).
- Vitamin K can be given in the outpatient setting either orally or subcutaneously. In patients with liver disease, there may be decreased absorption of dietary vitamin K
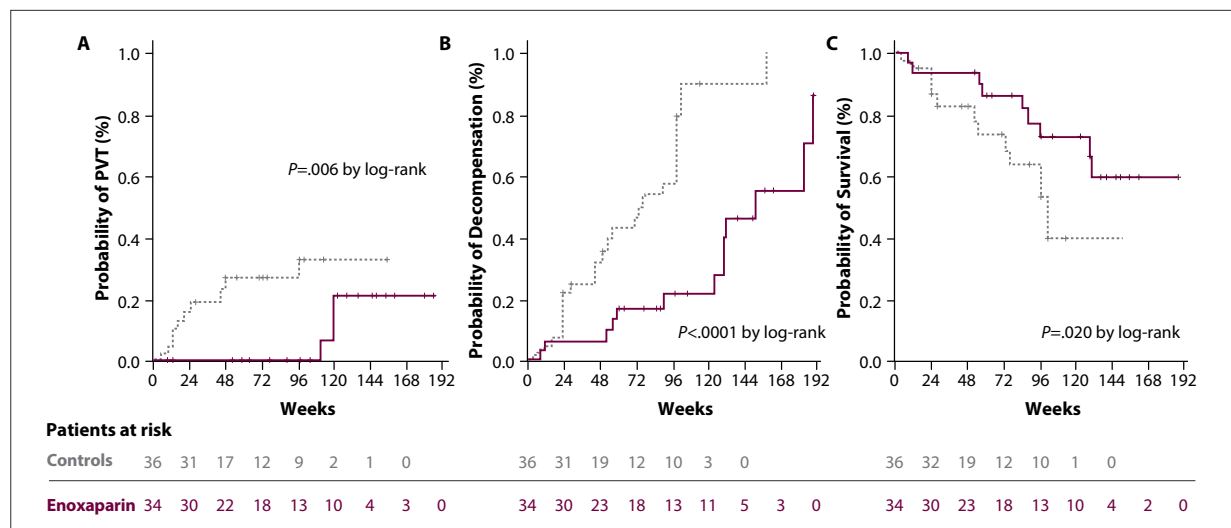
Figure 1. Actuarial probability of developing (A) portal vein thrombosis, (B) hepatic decompensation, and (C) probability of survival (dashed line: control group; continuous line: enoxaparin group). PVT, portal vein thrombosis. Adapted from Villa E et al. *Gastroenterology.* 2012;143(5):1253-1260.[1]

or oral supplements, and therefore parenteral administration (subcutaneous or intravenous) is preferred.

- Vitamin K administration will significantly reduce INR within 12 to 24 hours. If the INR becomes subtherapeutic following vitamin K substitution, raising it to therapeutic levels may take a week or longer, although this is less likely with vitamin K doses less than 5 mg.
- The daily risk of bleeding—even in patients with a high INR (4.0-10.0)—is low in noncirrhotic patients, but may be higher in cirrhotic patients with portal hypertension.
- Supratherapeutic INRs can be satisfactorily managed by holding warfarin, coupled with frequent monitoring if the patient is not at a high risk for bleeding or is actively bleeding.

Managing Patients With Nontherapeutic INRs

Some patients receiving long-term warfarin therapy are difficult to manage because they have unexpected fluctuations in their INRs. These fluctuations can be caused by several issues. One is as straightforward as an inaccurate INR test; evidence shows that variability in INR values between laboratories continues to remain unacceptably high.[5,6] Other causes relate to changes in vitamin K levels, including vitamin K availability (caused by increased or decreased vitamin K in the diet or the use of broad-spectrum antibiotics), vitamin K absorption (caused by gastrointestinal factors or drug effects), or vitamin K–dependent coagulation factor synthesis or metabolism (eg, liver disease, drug effects, or other medical conditions). Changes in warfarin absorption (caused by gastrointestinal factors or drug effects) or metabolism (by liver disease or drug effects) can also cause fluctua-

tions in INR. Finally, other factors such as undisclosed concomitant drug use or patient compliance issues (eg, surreptitious self-medication, missed doses, and miscommunication about the dose adjustment) can result in otherwise unexplained changes in INR.

Several recommendations should be considered when managing patients with an elevated INR in the outpatient setting. Regardless of the INR value, significant bleeding requires hospital admission and close evaluation as an inpatient.

For patients with an INR greater than the therapeutic level but below 5.0, who do not have significant bleeding, the dose should be lowered or omitted, and therapy should be resumed at a lower dose when the INR reaches the therapeutic range. For patients in whom the INR is only minimally higher than the therapeutic range, no dose reduction may be required. The INR should be rechecked in 1 to 2 days.

For patients with an INR over 5.0 but under 9.0 and who have no significant bleeding, one of several options may be appropriate. First, the next 1 to 2 doses of therapy may be omitted, while the INR is monitored frequently; therapy is then resumed at a lower dose when the INR reaches a therapeutic level. Another option is to omit the next dose and administer vitamin K (1-2.5 mg orally), particularly if the patient is at increased risk of bleeding. Finally, if a more rapid reversal is required, vitamin K (2-4 mg orally) should be administered, with the expectation that a reduction of the INR will occur within 24 hours. If the INR is still high, an additional dose of vitamin K (1 to 2 mg orally) may be appropriate.

For patients with an INR over 9.0 and with no significant bleeding, one of several options may be used.

Table 2. Common Drug and Food Interactions With Coagulation or Anticoagulation

Decreased Anticoagulation Effect (Causing a Lower INR)		
Induction of Enzymes	**Increased Procoagulant Effect**	**Decreased Drug Absorption**
Nafcillin Rifampin (common) Carbamazepine Phenytoin (late) Barbiturates Dicloxacillin Azathioprine Cyclosporine Trazodone	High vitamin K–content foods and enteral feeds Collards Kale Mustard and turnip greens Parsley Spinach Swiss chard Large amounts of avocado	Aluminum hydroxide Cholestyramine Sucralfate
Increased Anticoagulation Effect (Causing a Higher INR)		
Inhibit Metabolism		**Other**
Acetaminophen (>2 g/day) Acetylsalicylic acid Acute alcohol use (if concomitant liver disease) Amiodarone (common) Anabolic steroids Cimetidine Ciprofloxacin Clofibrate Clarithromycin Cotrimoxazole Erythromycin (common) Fluconazole Fluorouracil Flu vaccine Isoniazid (600 mg/d) Itraconazole	Ketoprofen Lovastatin Metolazone Metronidazole (common) Miconazole Nalidixic acid Norfloxacin Ofloxacin Omeprazole Piroxicam Propafenone Propoxyphene Quinidine Trimethoprim and sulfamethoxazole (common) Tamoxifen Tetracycline Voriconazole	Ethacrynic acid Sulfonamides Sulfonylureas Neomycin
Increased Bleeding Tendency (Without a Predominant Change in INR)		
Cephalosporins Clopidogrel NSAIDs	Heparin Enoxaparin Propranolol	Salicylates Glucagon Quinidine

INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

First is to halt warfarin therapy and administer a dose of vitamin K (3 to 5 mg subcutaneously), with the expectation that the INR will be reduced substantially in 24 to 48 hours. The INR should be monitored frequently, and additional vitamin K administered if necessary. Once the INR reaches a therapeutic level, therapy can be resumed at a lower dose. Alternatively, consider admission for close observation or fresh frozen plasma (FFP) transfusion if the patient is at high risk for bleeding, and/or if the patient has significant comorbidities. In these cases, it may be possible to use TEG/ROTEM to roughly guide therapy. For example, if the INR is 9 and the R value is normal, then no FFP is needed.

For patients with subtherapeutic INR levels, it is first important to isolate the cause of the reduction of a previously therapeutic INR. Possible causes to consider include diet, medication noncompliance, and new medications. Pending understanding of the underlying cause, the dose of warfarin may be increased. The INR level should then be rechecked in 1 to 2 days. It may also be necessary to consider bridging therapy with LMWH or unfractionated heparin, depending on the patient's risk for thromboembolism.[7]

Newer Anticoagulation Medications

Warfarin has traditionally been the anticoagulant agent of choice for the treatment and prevention of thrombotic

complications in patients with liver disease. However, the use of warfarin in routine clinical practice remains a challenge due to its narrow therapeutic index, particularly in patients with liver disease. This may result in supratherapeutic or subtherapeutic INR levels.

Other anticoagulation agents that have also been used include LMWH, acetylsalicylic acid, and clopidogrel. Over the past decade, a number of newer anticoagulation agents have emerged and are often preferred to warfarin due to better efficacy and safety profiles. These agents, which include apixaban, dabigatran, edoxaban, and rivaroxaban, are currently recommended as first-line treatment or alternatives to warfarin in the management of atrial fibrillation and venous thromboembolism in numerous guidelines from North America and Europe. The efficacy and safety of these drugs in the setting of liver disease have not been well studied, although clinical use is becoming more frequent. Each of these agents is subject to some degree of hepatic metabolism, and therefore decreased liver function may affect their availability and effectiveness. In one recommended approach, all of the newer anticoagulation agents, as well as warfarin (INR 2-3), can be used in patients with Child-Pugh A disease.[8] For patients with Child-Pugh B disease, all newer anticoagulation agents (with the exception of rivaroxaban) may be used with caution, and warfarin (INR 2-3) may also be used. None of the newer anticoagulation agents are recommended in patients with Child-Pugh C disease; warfarin (INR 2-3) is still recommended, although without clear data to support this contention.

Adverse Events of Anticoagulation Medications

According to the US Centers for Disease Control and Prevention, oral anticoagulants are the most common causes of adverse drug events leading to emergency room visits and emergent hospitalizations among older adults (≥65 years).[9] In 2017, bleeding from oral anticoagulants resulted in approximately 235,000 emergency department visits.[10] Bleeding is the primary adverse event of concern associated with the use of anticoagulation medications, and these events can be categorized as either a minor hemorrhage or a major hemorrhage.

There is no well-established definition as to what constitutes a minor hemorrhage event. Minor events are small bleeding episodes that resolve spontaneously or promptly with pressure. Examples may include epistaxis that is stopped with local pressure or a single blood-streaked stool (as opposed to frank melena or hematochezia). No systemic symptoms of acute blood loss, such as lightheadedness, dizziness, weakness, palpitations, and pallor, should be present. Minor bleeding events do not require

cessation or reversal of anticoagulation if warfarin is in the target range. A follow-up phone call with the patient is indicated to ensure that the bleeding symptoms abated. Bleeds that appear minor but co-occur with systemic symptoms should be subjected to the same evaluation as major bleeds.

A major hemorrhage is a potentially life-threatening event that requires immediate attention. Examples of major bleeding events include gastrointestinal bleeding, intracranial hemorrhage, muscle bleeds, and extensive hematomas. Major bleeding events warrant immediate evaluation and treatment in an emergency department. Admission for further evaluation and identification of the bleeding source may be necessary. Interventions include reversal of anticoagulation, consisting of vitamin K and blood product transfusion (FFP or prothrombin complex concentrates, and possibly packed red blood cells).

START-Events, a branch of the START registry (Survey on Anticoagulated Patients Register), was a prospective, observational, multicenter, international study designed to evaluate the actual management of bleeding or recurrent thrombotic events in routine clinical practice.[11] Testa and colleagues published an evaluation of the management of 117 bleeding patients between January 2015 and December 2016. Among these patients, 53 had intracranial bleeding (13 fatal), 42 had gastrointestinal bleeding (1 fatal), and 22 had bleeding in other sites. Therapeutic interventions were undertaken in 71% of patients for the management of bleeding.[11] These therapeutic strategies included fluid replacement or red blood cell transfusion, prothrombin complex concentrates, antifibrinolytic drugs, and the administration of idarucizumab.

Although cirrhotic patients may have an increased risk for a bleeding event, several recent studies of anticoagulation in those with advanced fibrosis or cirrhosis appear to demonstrate acceptable safety profiles. A retrospective case series of hospitalized cirrhotic patients receiving thromboprophylaxis suggested that gastrointestinal bleeding risk appears to be similar to those patients not receiving prophylactic anticoagulation.[12] This case series reported a rate of gastrointestinal bleeding of 2.5% and a rate of major bleeding below 1%. Cerini and colleagues evaluated the impact of anticoagulation therapy on upper gastrointestinal bleeding, predominantly due to portal hypertension in cirrhotic patients.[13] This study demonstrated that the use of anticoagulation therapy did not influence outcome—as measured by mortality, use of rescue therapy, intensive care admission, transfusion requirement, or length of hospital stay—when matched to cirrhotic patients who were not receiving anticoagulation therapy. Preliminary results from a United Kingdom–based multicenter study evaluating the antifibrotic effects

of warfarin anticoagulation in patients with chronic hepatitis C virus infection did not report an increased risk of bleeding.[14]

Over the years, certain risk factors for bleeding events during anticoagulation therapy have been identified. One of these is the intensity of anticoagulant therapy, which has been demonstrated to be the most important risk factor for bleeding.[15] The risk of bleeding increases exponentially as the INR exceeds 5.0, when the risk becomes clinically unacceptable in noncirrhotic patients. Patient characteristics are another important factor impacting the risk of bleeding on anticoagulation therapy.[16-23] Some of these characteristics include older age, female sex, history of bleeding, peptic ulcer, active cancer, hypertension, prior stroke, renal insufficiency, alcohol abuse, and liver disease.

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Correction of Coagulopathy of Liver Disease Prior to Procedures

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The correction of abnormal hemostatic parameters in liver disease by blood- and plasma-products (such as thrombopoietin [TPO] agonists, platelets and fresh frozen plasma [FFP] infusions, prothrombin complex concentrate, and cryoprecipitate), especially prior to procedures, poses a challenge for the managing physician. Evidence in support of routine correction of in vitro clotting abnormalities is largely lacking. In fact, clinical evidence generally supports the detrimental effects encountered with transfusion of blood and plasma-products. Types of transfusion reactions include acute hemolytic, delayed hemolytic, febrile nonhemolytic, anaphylactic, simple allergic, septic (bacterial contamination), transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO). Clinicians must also be aware that transfusion of plasma may increase portal pressure, and thereby raise the risk of recurrent portal hypertensive bleeding.[1,2] When a reaction is suspected, the transfusion should be stopped immediately, and the blood bank and treating clinician should be notified.[3] In general, default normalization of hemostatic parameters in liver disease (with or without procedures) is not indicated. Any transfusion intervention should be weighed carefully for risks and benefits on an individual basis.

This article provides information on coagulation correction prior to commonly performed procedures in patients with coagulopathy due to liver disease. An algorithm for the management of thrombocytopenia in patients with chronic liver disease is shown in Figure 1.[4,5] There are currently no data to suggest fixed cutoffs of prothrombin time/international normalized ratio (INR), partial thromboplastin time, or platelet count for various procedures. In general, use of recombinant human factor VIIa or activated prothrombin concentrates is discouraged due to the high possibility of thrombotic complications. Unless a bleeding tendency is clinically apparent, the routine use of FFP is also discouraged. A strategy incorporating the use of stand-by products if bleeding occurs may be a safe alternative.

Risk of Bleeding With Invasive Procedures

Different procedures are associated with a varied risk of bleeding in patients with liver disease (Table 1).[6] This risk is further complicated by factors related to the individual patient. For example, one study evaluated the incidence of bleeding following invasive procedures in 121 patients with advanced liver disease who had thrombocytopenia.[7] In this study, thrombocytopenia (present in 84% of

Table 1. Bleeding Risk According to Type of Procedure

Lower-Risk Procedures	Intermediate-Risk Procedures	Higher-Risk Procedures
Diagnostic EGD or colonoscopy	PEG	Complicated polypectomy
Variceal ligation	Cystogastrostomy	EMR or ESD
Uncomplicated polypectomy	Biliary sphincterotomy	NOTES
Paracentesis	Percutaneous or transjugular liver biopsy	All major surgery (cardiac, abdominal, orthopedic)
Thoracentesis	Percutaneous biopsy of extrahepatic organ	Brain or spinal surgery
Dental extraction	Transjugular intrahepatic portosystemic shunt	Intracranial pressure catheter insertion
Cardiac catheterization	Transarterial or percutaneous HCC therapies	
Central line placement	Lumbar puncture	

EGD, upper endoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HCC, hepatocellular carcinoma; NOTES, natural orifice translumenal endoscopic surgery; PEG, percutaneous endoscopic gastrostomy.

Adapted from Intagliata NM et al. *Thromb Haemost.* 2018;118(8):1491-1506.[6]
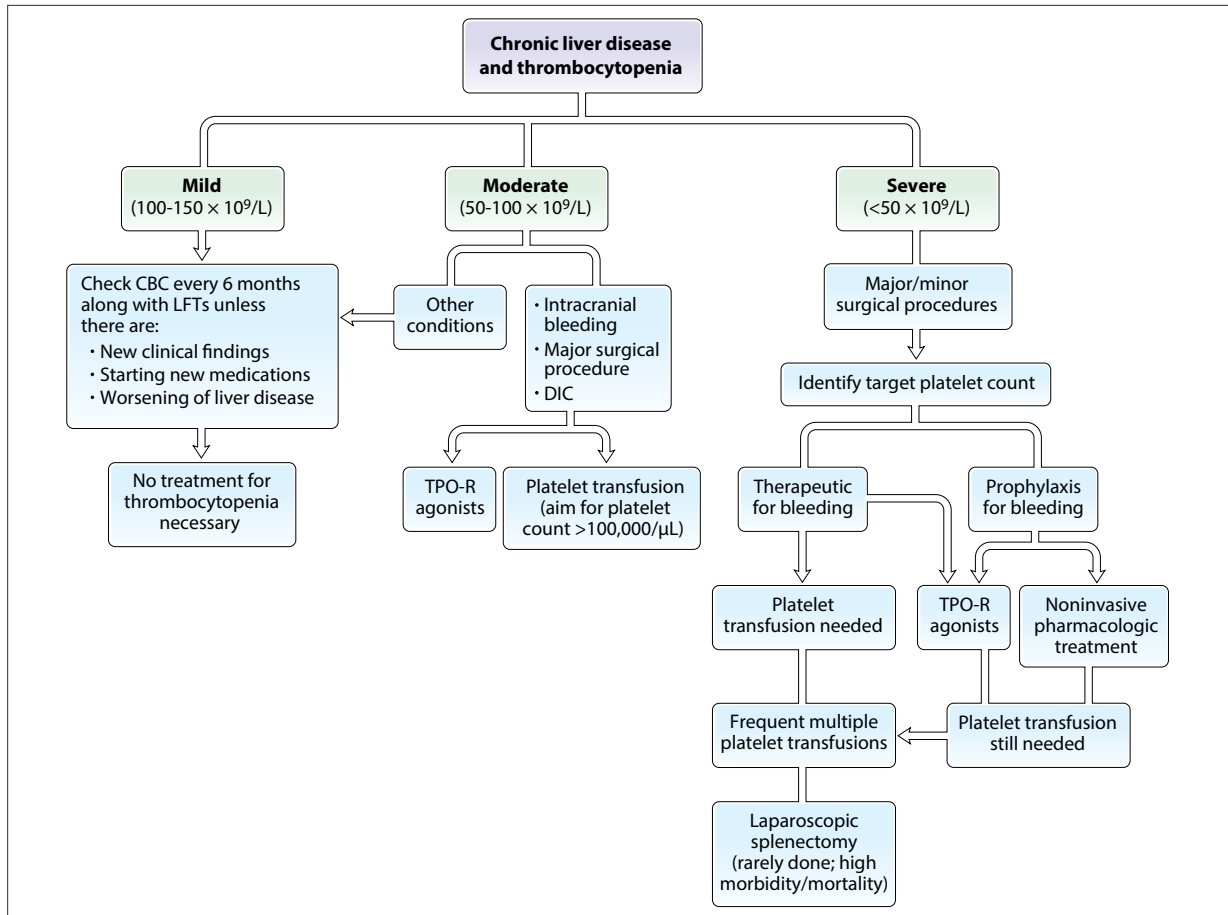
Figure 1. An algorithm for the management of thrombocytopenia in patients with chronic liver disease. CBC, complete blood count; DIC, disseminated intravascular coagulation; LFT, liver function tests; TPO-R, thrombopoietin receptor. Adapted from Saab S, Brown RS Jr. *Dig Dis Sci*. 2019;64(10):2757-2768[4] and Gangireddy VG et al. *Can J Gastroenterol Hepatol*. 2014;28(10):558-564.[5]

patients) was defined as a platelet count of less than 150,000/μL, and severe thrombocytopenia (present in 51% of patients) was defined as a platelet count of less than 75,000/μL. Among the 102 patients with thrombocytopenia, 49% underwent an invasive procedure (64% with severe thrombocytopenia). Bleeding occurred in 31% of patients with severe thrombocytopenia who underwent an invasive procedure, and in none of those with moderate thrombocytopenia. A post hoc analysis of patients with advanced hepatic fibrosis and cirrhosis in the HALT-C trial also suggested that bleeding complications of liver biopsy were more common in patients with platelet counts below 60,000/μL.[8] These clinical observations support an in vitro study in which a platelet count of 56,000/μL or higher in cirrhotic patients supported thrombin generation at the 90th percentile of patients with no liver disease.[9] Thus, there appears to be general agreement that a platelet count of less than 60,000/μL should prompt consideration of repletion before invasive procedures, particularly those associated with a moderate-

to-high risk of bleeding.

Use of TEG (Thromboelastography) and ROTEM (Rotational Thromboelastometry)

The overall goal in patients with liver disease who appear to be at increased risk of bleeding is to appropriately apply coagulation products and reduce the risk of volume overload, transfusion-transmitted diseases, transfusion reactions, blood sensitization, and other complications of blood product infusion. An elastography decision tree is shown in Figure 2. TEG/ROTEM are whole blood clotting assays with proven clinical utility to manage blood product replacement during specific surgical procedures, including liver transplant.[10] However, TEG and ROTEM are not sensitive to the activity of levels of the natural anticoagulants protein C, protein S, and anti-thrombin, nor do they include endothelial proteins in the reaction mixture (eg, thrombomodulin, the endogenous activator of protein C). Thus, these tests may be useful as screening
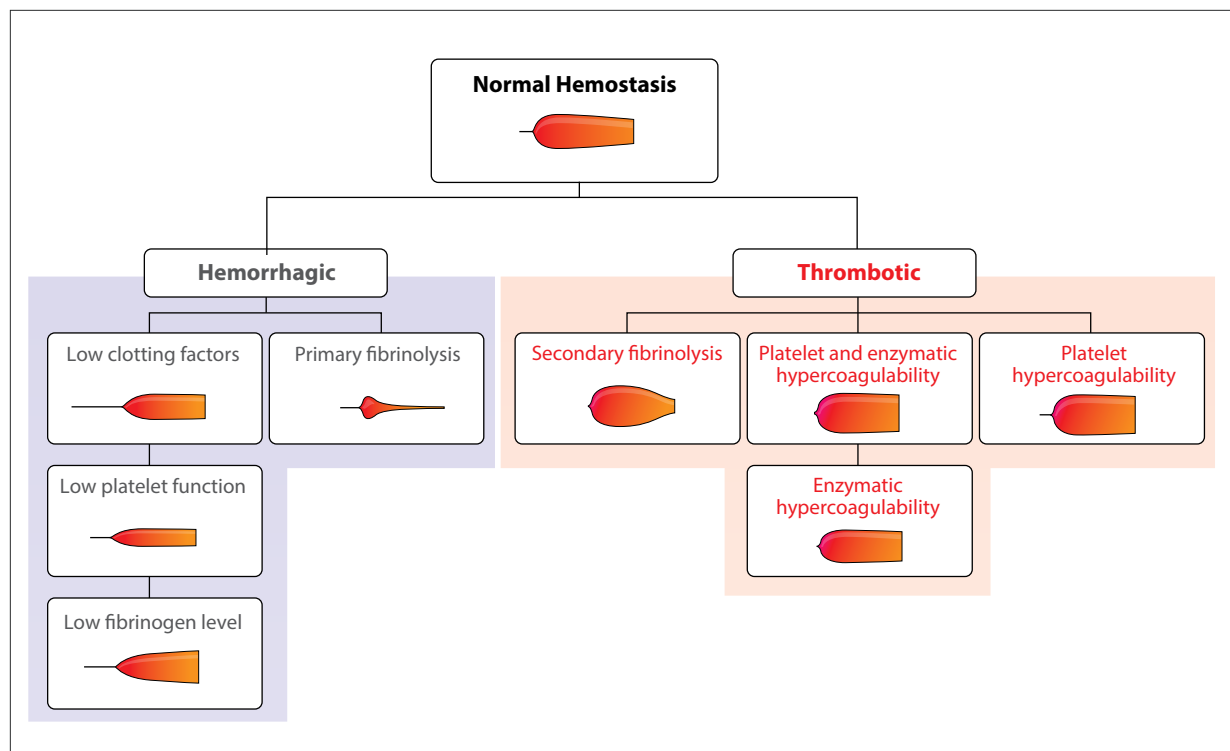
Figure 2. Elastography decision tree.

tools for time to clot formation, clot expansion, platelet activity, and fibrinolysis, but may overestimate pro-hemostatic potential because they are relatively insensitive to the anticoagulant pathways.

An elevated INR in acute liver failure is an integral part of the definition of the syndrome, is proportional to the severity of liver injury and likelihood of death, and historically has been considered "a predictor" of increased bleeding risk. However, an analysis of more than 1800 patients with acute liver failure has refuted the latter, as there was no relationship between the INR and bleeding complications, which were uncommon (~10%) and usually clinically insignificant.[11] In contrast, severe thrombocytopenia is a risk factor for both death and bleeding complications in patients with acute liver failure, probably because it is a marker of more severe systemic inflammation.[12] Early studies of patients with acute liver failure failed to show a difference in TEG parameters in those with or without bleeding complications, or between those who recovered with their native liver or died/received a liver transplant.[13,14] These studies, however, were likely underpowered. A study of 200 patients from the Acute Liver Failure Study Group using ROTEM, however, suggested that hypocoagulable ROTEM parameters are more frequently observed in patients with severe liver injury, systemic inflammation, and systemic complications, including bleeding and death.[15] Interest-

ingly, TEG and ROTEM have shown that a significant proportion of patients with acute liver failure may also exhibit a hypercoagulable state, and thrombotic complications (eg, splanchnic vascular thromboses) were noted in a significant minority. Thus, patients with acute liver failure most frequently do not have a clinically significant hypocoagulable state and in fact may be hypercoagulable. Those with the most severe liver injury have the most hypocoagulable hemostatic profile according to ROTEM, but it remains to be determined whether such patients should have ROTEM parameters corrected prior to invasive procedures. TEG/ROTEM data can be adjusted for native vs functional fibrinogen using trends in published conversion data.[16]

TEG may have a role in decreasing prophylactic blood component transfusions in patients with cirrhosis, as shown in a randomized controlled trial.[17] In this study, cirrhotic patients with "severe coagulopathy" (defined as an INR >1.8 and/or platelet count <50,000/μL) were randomly assigned to standard-of-care plasma and platelet transfusions or transfusions based upon TEG parameters. Receipt of plasma and/or platelets was reduced from 100% in the standard-of-care group to 16.7% in the TEG group. Importantly, there were no bleeding complications in the TEG group, and cumulative survival rates of the groups were similar. This study was the first to show that TEG-based decisions regarding the need for platelet and/

Table 2. TEG in Patients With Liver Disease

Review previous TEGs to determine if the patient is currently receiving heparin for correction of secondary fibrinolysis
Basic TEG
If any blood products are given, rerun basic TEG
R–Coagulation Factors (5-10 min reference range)
• <5 min hypercoagulable
• 10-12 min: consider 1u FFP[a]
• 13-15 min: consider 2u FFP[a]
• >15 min: consider 3u FFP[a]
K/Angle–Fibrinogen
• If R and MA are normal and K and angle are abnormal: consider cryo
• (K 1-3 min reference range) (angle 53-72 degrees reference range)
• K >3 min: consider 1-2 prepooled units cryo
• Angle <53 degrees: consider 1-2 prepooled units cryo
• Recheck if cryo has been given and patient is not improving, consider platelets
MA–Platelet Function (50-70 reference range bleeding)
• 48-50 mm: Consider 0.3 mcg/kg DDAVP, especially in the presence of uremia
• ≤47 mm: Consider 1 u platelets
MA–Prior to Invasive Procedure
• If platelet count is <20,000 and MA <60: consider TPO agents if time to plan the procedure or 2 U SDP
• If platelet count is between 20,000 and 60,000 and MA is <60 and a procedure is planned, use TPO agonist to avoid platelet transfusions if time to plan the procedure or 1 U SDP
LY30–Fibrinolysis (0%-8% reference range)
• Normal R, K, and angle, MA <50, LY30 >5% = primary fibrinolysis: consider antifibrinolytic agents (tranexamic acid, aminocaproic acid)
• R <5, K <1.0 min: angle >72, MA >70, LY30 >5% = DIC stage 1/ Secondary Fibrinolysis: Consider heparin (can be considered in bleeding patient)
TEG With Heparinase
If the heparin R time significantly differs from the basic TEG R time (heparin effect), use the basic TEG R time value:
• 10-15 min: consider protamine (15 mg)
• 15-20 min: consider protamine (20 mg)
• 20-25 min: consider protamine (25 mg)
• >25 min: consider protamine (30 mg)
• If protamine is given, rerun both basic TEG and TEG with heparinase to ensure Δ R time <1 min

Cryo, cryoprecipitate; DDAVP, desmopressin; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; K, clot kinetics, measuring time taken for a certain level of clot strength to be reached; LY30, clot lysis at 30 minutes after maximum clot strength; MA, maximum amplitude; R, measure of coagulation time from start to initial fibrin formation; SDP, single donor platelet; TEG, thromboelastography; TPO, thrombopoietin.

[a]If the patient is receiving treatment with a novel oral anticoagulant, see anticoagulation reversal guidelines or call the pharmacy.

or plasma transfusions prior to invasive procedures are safe in certain patients with cirrhosis.

In summary, TEG/ROTEM may be useful in acute and chronic liver disease patients to help determine the functional significance of an elevated INR/prothrombin time (PT) and low platelet count, long-considered a state of "autoanticoagulation." It should be emphasized that patients with liver disease experience few spontaneous bleeding events, and that in the majority of patients with cirrhosis, bleeding is related to portal hypertension. Furthermore, portal hypertensive bleeding is a matter of portal pressure, not abnormal hemostasis, as was conclusively shown by the lack of protection conferred by recombinant factor VII against variceal rebleeding.[18,19] However, formal guidelines for the use of TEG in patients with liver disease undergoing invasive procedures have not been rigorously tested.

Table 2 lists an approach to determining which patients may benefit from pro-hemostatic blood component repletion. Every center will have its own protocol, and the specific parameters will depend upon whether the TEG is "native" or kaolin-stimulated. Basic TEG should be defined. The most common cause of the heparin effect is probably sepsis (due to release of endogenous heparinoids), rather than heparin administration.

Baseline TEG should include the basic procedure and TEG with heparinase. Fibrinolysis is generally defective in acute liver failure primarily because of low plasminogen. Sepsis should be considered if there is evidence of the heparin effect. If the heparin R time significantly differs from the basic TEG R time (the heparin effect), the basic TEG R time value should be used. The use of protamine should be considered in consultation with the expert guidance of a hematologist.

Interventions to Prevent Bleeding

In the setting of an abnormal TEG, 3 main interventions are used (Table 3): platelet transfusion, FFP, and cryoprecipitate. Platelet transfusions, alone or in combination with other blood components, are most effective for improving abnormal TEG variables in critically ill patients with coagulopathy and liver disease. In fact, in one study, platelet transfusions had a greater impact on clot strength than fibrinogen or procoagulant factor levels.[20] This study enrolled 60 critically ill patients with a coagulopathy and liver disease. Only platelet transfusions were significantly associated with an improvement in TEG variables. Each unit of platelets was associated with a significant decrease in both the reaction and thrombin constant time, an increase in the alpha angle, and an increase in the maximum amplitude.

Plasma transfusions remain of uncertain benefit

before invasive procedures. In a recent study of 53 patients with cirrhosis and a mean INR of 2.2, the administration of plasma enhanced thrombin generation by only 5.7%, and corrected the INR to normal in fewer than 2%.[21] Furthermore, plasma transfusion worsened thrombin generation in 34%, presumably because plasma contains significant amounts of protein C. Since plasma transfusion has not been shown to reduce bleeding complications after invasive procedures in patients with cirrhosis, these data strongly refute the practice of routinely correcting the INR.

In addition, thrombopoietin receptor agonists (TPO-RAs) can have a role in the prevention of bleeding and the decreased use of blood products. According to the American Gastroenterological Association Clinical Practice Update on coagulation in cirrhosis, TPO-RAs can be used as an alternative to platelet transfusion for elective procedures. However, they require time (about 5-10 days) to elevate platelet levels.[22] Two TPO-RAs, avatrombopag and lusutrombopag, are indicated in the setting of thrombocytopenia in patients with chronic liver disease for use prior to a procedure. Importantly, the effect of these agents lasts much longer than a platelet transfusion—2 weeks rather than 2 hours. Two others, romiplostim and eltrombopag, are approved by the US Food and Drug Administration for other indications. There are currently no prospective trials using TEG or ROTEM to guide management with TPO-RAs. Future research is needed on how to use TEG or ROTEM to decrease platelet transfusions and to decide when to use TPO-RAs.

Management of Oral Anticoagulation Prior to Invasive Procedures for Cirrhotic Patients

Several modes for maintaining anticoagulation for the longest possible time prior to an invasive procedure exist. Cirrhotic patients' baseline INR values are usually higher than 1.5, but this correlates poorly with bleeding risk, and correction with FFP should be considered only if the R value is prolonged in TEG/ROTEM.[23] This is emphasized here with the known risk of FFP being an "anticoagulant" in some patients and associated with risks of transfusion reactions. However, FFP use should be executed with caution after a clinical risk/benefit assessment for detrimental consequences from fluid overload, TRALI, TACO, and thromboembolism. Generally, anticoagulants can be restarted within 12 to 24 hours after most procedures, if there is no bleeding.

The generally accepted risk stratifications used to categorize noncirrhotic patients according to bleeding risk may be less useful in patients with cirrhosis because high-quality controlled trials are lacking.

Table 3. Potential Interventions in the Setting of Abnormal TEG

Intervention	Notes
Platelets/TPO	• For low-risk procedures: no transfusion or TPO • For moderate-risk procedures: <20 k/MA<60 • For high-risk procedures: <50 k/MA<60 • Balance TPO choice with transfusion risks • TPO preferred for planned procedures • Platelet transfusion only an option for emergency or urgent procedures
Fresh frozen plasma	• Lack of predictable effect: conventional doses correct in only 10% to 12% of cirrhotic patients • In a patient with INR higher than approximately 2 to 3 undergoing a high-risk procedure, consider 2 units of plasma and proceed immediately to the procedure. Do not repeat the INR. • See Table 2 • Balance with transfusion risks
Cryo	• If low fibrinogen (K >3 or angle <53)

Cryo, cryoprecipitate; K, clot kinetics, measuring time taken for a certain level of clot strength to be reached; INR, international normalized ratio; MA, maximum amplitude; TEG, thromboelastography; TPO, thrombopoietin.

Those with a low risk of thromboembolism include patients who did not experience a venous thromboembolism in the preceding 12 months and patients with atrial fibrillation who do not have a history of stroke. Those with a high risk of thromboembolism include patients with a recent (<3 months) history of venous thromboembolism, patients with high-risk thrombophilias, and patients with a mechanical cardiac valve in the mitral position or an old model cardiac valve.

The most common indications for anticoagulation specifically in cirrhotic patients and recently transplanted patients include portal vein thrombosis, hepatic artery dissection, and hepatic artery thrombosis. TEG/ROTEM testing along with INR/PT correlation and clinical risk assessment is recommended prior to any intervention. Although there are no set guidelines for these specific conditions, the scenarios in Table 4 show some methods for managing anticoagulation prior to an additional invasive procedure.[24]

TEG and ROTEM are not sensitive enough to anticoagulants to be useful in this setting. Low-molecular-weight heparin is commonly used as bridging anticoagulation for patients receiving warfarin since it can safely and conveniently be administered in the outpatient setting. Parenteral unfractionated heparin should be used

Table 4. Scenarios for Managing Anticoagulation Prior to an Invasive Procedure[a]

Scenario	Intervention
Low risk for thromboembolic event (VTE >12 months ago; no history of thrombophilia)	Warfarin • Stop warfarin 5 days before procedure • Run basic TEG to determine bleeding risk on the morning of a high-risk procedure • Consider INR/PT test and correlate with TEG testing • Resume warfarin on day of procedure • Bridging anticoagulation is generally not indicated DOAC[b] • Minimal-risk procedure: Hold on day of procedure only • Low/moderate-risk procedure: Hold dose starting 1-2 days before procedure, resume 1-2 days after procedure • High-risk procedure: Hold dose starting 2-4 days before procedure, resume 2 days after procedure
Moderate risk for thromboembolic event (VTE 3-12 months ago; thrombophilias other than antiphospholipid antibody syndrome)	Warfarin • Stop warfarin 5 days prior to procedure • Run basic TEG to determine bleeding risk on the morning of the procedure[a] • Consider INR/PT test and correlate with TEG testing • Resume warfarin on day of procedure • Consider postoperative bridging LMWH[c] starting 12-24 hours after procedure • LMWH can be stopped when INR/PT >2 DOAC[b] • Minimal-risk procedure: Hold on day of procedure only • Low/moderate-risk procedure: Hold dose starting 1-2 days before procedure, resume on day after procedure • High-risk procedure: Hold dose starting 2-4 days before procedure, resume 2 days after procedure
High risk for thromboembolic event (VTE in last 3 months; mechanical heart valve, AFib with history of stroke, antiphospholipid antibody syndrome)	Warfarin • Stop warfarin 4-5 days prior to procedure • Start bridging LMWH[c] 2-3 days prior to procedure • Hold LMWH 24 hours before procedure • Run basic TEG to determine bleeding risk on the morning of the procedure[a,d] • Consider INR/PT test and correlate with TEG testing • Resume warfarin on day of procedure • Resume bridging LMWH[c] 12-24 hours post-procedure • LMWH can be stopped when INR/PT >2 DOAC[b] • Minimal-risk procedure: Hold on day of procedure only • Low/moderate-risk procedure: Hold dose starting 1 day before procedure, resume on day after procedure • High-risk procedure: Hold dose starting 2 days before procedure, resume 1-2 days after procedure

[a]There is little direct correlation between R-time and INR.

[b]Intervals may need to be adjusted according to renal and hepatic function.

[c]For patients with CrCl <30, use unfractionated heparin for bridging.

[d]For risk management.

AFib, atrial fibrillation; CrCl, creatinine clearance; DOAC, direct oral anticoagulants; INR/PT, international normalized ratio/ prothrombin time; LMWH, low-molecular-weight heparin; R, measure of coagulation time from start to initial fibrin formation; TEG, thromboelastography; VTE, venous thromboembolism. Adapted from Tafur A, Douketis J. *Heart.* 2018;104(17):1461-1467.[24]

instead in patients with advanced renal disease (creatinine clearance <30). In patients at high risk of bleeding, unfractionated heparin is often used due to its short half-life and reversibility with protamine. Monitoring heparin therapy in patients with advanced liver disease is challenging. Due to impaired synthesis of clotting factors, activated partial thromboplastic time (aPTT) is often exquisitely sensitive to heparin products and may overestimate the degree of therapeutic anticoagulation. Instead, anti-Xa monitoring is the preferred approach. Please note, when antithrombin is not added to the assay, anti-Xa levels can underestimate the effect of heparin due to impaired synthesis of antithrombin in patients with liver disease. Anti-Xa monitoring has not been validated for direct Xa inhibitors such as rivaroxaban and apixaban and should not be used to guide therapy with these agents. Table 5 lists reference

Table 5. Reference Values for Patients Requiring DVT
Prophylaxis

Intervention	Reference Values
IV therapeutic unfractionated heparin	• 0.3-0.7 anti-Xa U/mL plasma
Prophylactic unfractionated heparin	• 0.2-0.4 anti-Xa U/mL plasma
Low-molecular-weight heparin (enoxaparin)	• 0.5-1.0 anti-Xa U/mL plasma for therapy when injected twice a day; draw 4 hours after injection • 1.0-2.0 anti-Xa U/mL plasma for therapy when injected once a day; draw 4 hours after injection • 0.2-0.4 anti-Xa U/mL plasma for prophylaxis; draw 4 hours after injection

DVT, deep vein thrombosis; INR, international normalized ratio; IV, intravenous.

values for anti-Xa monitoring.

TEG and ROTEM in the acute setting have been shown to decrease the need for blood product transfusions, and thereby decrease the incidence of TRALI and other transfusion-related reactions, including infections. For example, in one study of 96 patients with cirrhosis and nonvariceal upper gastrointestinal bleeding with significant coagulopathy (defined in this study as INR/PT >1.8 and/or a platelet count of <50 × 10^9/L), patients were randomly assigned to a group treated with a TEG-guided transfusion strategy or a group in which transfusion was guided by traditional laboratory measures (the standard-of-care group).[25] All 3 blood components (FFP, platelets, and cryoprecipitate) were received by 26.5% of patients in the TEG-guided group compared with 87.2% of patients in the standard-of-care group (*P*<.001). All 47 patients in the standard-of-care group required a blood component transfusion, whereas 7 of the 49 patients in the TEG group received no blood component transfusion. There was also significantly lower use of blood components in the TEG group compared with the standard-of-care group. Overall, this study found that a TEG-guided transfusion strategy leads to a significantly lower use of blood components compared with transfusion guided by INR/PT and platelet count, without increases in failure to control bleeds, failure to prevent rebleeds, and mortality.

Venous Thromboembolism Prophylaxis in Patients With Liver Disease or Cirrhosis and Portal Hypertension

Patients with liver disease undergoing procedures have the same or even increased risk for venous thromboembolism as compared with other patients. However, prolongation of INR/PT, aPTT, or thrombocytopenia often creates uncertainty regarding the relative bleeding risks with anticoagulation and the appropriate monitoring of anticoagulation. Patients with cirrhosis, portal hypertension, and/or low platelet counts due to portal hypertension should undergo standard postprocedure prophylactic anticoagulation as defined for noncirrhotic patients. Often, this strategy includes daily low-dose enoxaparin or unfractionated heparin 2 or 3 times daily. Please note, patients with cirrhosis/portal hypertension should undergo routine outpatient esophagogastroduodenoscopy assessment and undergo prophylactic banding if the varices are larger than 1+ to minimize risk of bleeding. Although no studies support this practice, it is common.

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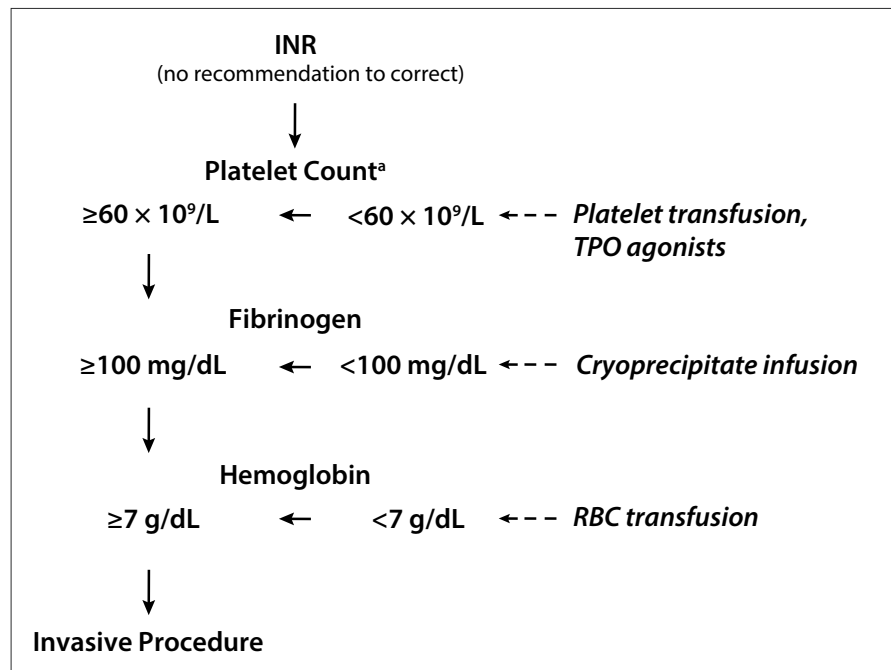
Current Observations in the Management of Hypo- and Hypercoagulability in Patients With Acute or Chronic Liver Failure

Robert G. Gish, MD, and Joel M. Brothers, MD

Summary and Key Points

- Patients with cirrhosis are often hypercoagulable, and thus need surveillance for portal vein thrombosis using Doppler ultrasound every 6 months.

- All patients with cirrhosis or acute liver failure in the emergency room or inpatient service who are bleeding or require an invasive procedure should undergo a thromboelastography (TEG)/rotational thromboelastometry (ROTEM) on evaluation if available and then be scheduled for monitoring of their clinical status. Consider TEG/ROTEM on an individualized basis for other patients. If TEG/ROTEM is not available, integrate the international normalized ratio (INR), platelet count, and fibrinogen with risk of bleeding, risk of transfusion-related acute lung injury (TRALI)/transfusion-associated circulatory overload, and other transfusion risks, based on the knowledge that INR is a poor signal of coagulation balance (Figure 1).

- TEG/ROTEM may supersede clinical decisions with the INR/prothrombin time (PT) and may eventually make the INR/PT superfluous. The TEG/ROTEM can be supplemented by platelet count and fibrinogen in patients with cirrhosis or acute liver failure.

- Patients with new evidence of portal vein thrombosis should be anticoagulated unless unstable. Among patients with cirrhosis who have an old portal vein thrombosis as documented by cavernous transformation of the portal vein with no fresh clot, a hypercoagulation phased workup should be considered to target the correct anticoagulation treatment and establish a correct risk and diagnosis. If there is evidence that the clot is progressing, strongly consider anticoagulation. Patients with cirrhosis develop portal vein thrombosis far more frequently from sluggish portal flow, hepatocellular carcinoma, and/or abdominal infection rather than a defined hypercoagulable state, which is difficult to evaluate.

Figure 1. An algorithm for the management of coagulation disorders in patients with liver disease. INR, international normalized ratio; RBC, red blood cell; TEG, thromboelastography; TPO, thrombopoietin. [a]Please see the article on background and evaluation of hypercoagulability for more information regarding the INR for TEG. Adapted from Stravitz RT. *Hepatol Int.* 2018;12(5):390-401.[13]

INR
(no recommendation to correct)

↓

Platelet Count[a]

≥60 × 10⁹/L   ←   <60 × 10⁹/L   ← – –   *Platelet transfusion, TPO agonists*

↓

Fibrinogen

≥100 mg/dL   ←   <100 mg/dL   ← – –   *Cryoprecipitate infusion*

↓

Hemoglobin

≥7 g/dL   ←   <7 g/dL   ← – –   *RBC transfusion*

↓

Invasive Procedure

- Patients with cirrhosis are probably at the same or higher risk for deep venous thrombosis and pulmonary embolism as other patients; deep venous thrombosis prophylaxis needs to be planned and individualized based on risk.

- Coagulation support for patients with liver disease should not be focused on the INR/PT, nor should fresh frozen plasma be used arbitrarily to "correct" the INR/PT; instead, the best approach is to replace the INR/PT test with TEG testing as soon as the TEG/ROTEM device is available.

- Evaluate the platelet count in all patients; if the platelet count is under 60,000 cells/uL, assess with TEG if available and use thrombopoietin receptor agonists (TPO-RAs) according to platelet level and risk of bleeding with procedures; if available, adjust TPO-RA use depending on the maximum amplitude on the TEG device.

- In the era of the COVID-19 pandemic, planning procedures in order to minimize time in an infusion center would support the use of a TPO-RA among patients at risk of thrombocytopenia.

Controversies

There is disagreement among the authors regarding the scope of laboratory testing that should be performed to identify hypercoagulable disorders in patients with cirrhosis and a history of thromboembolism. RG advocates for multiphase hypercoagulable testing in all patients with cirrhosis and portal vein thrombosis, Budd-Chiari syndrome, pulmonary embolism, deep venous thrombosis, or another major clotting episode. He argues that an acquired or inherited thrombophilia can be identified in the majority of patients in whom testing is performed, which can inform the need for genetic testing/counseling, the intensity of periprocedural venous thromboembolism prophylaxis, and the frequency of surveillance for clotting complications post-transplant. JB argues for a more tailored approach. In his opinion, portal vein thrombosis is common in patients with portal hypertension in the absence of a thrombophilia and does not necessarily warrant hypercoagulable testing. Tests such as protein C, protein S, antithrombin, and factor VIII are often positive in patients with cirrhosis due to impaired synthetic function (and enhanced endothelial production in the case of factor VIII) even in the absence of an inherited disorder, confounding interpretation of results. JB advocates hypercoagulable testing when one of the following criteria is met: 1) it affects choice of anticoagulation (ie, warfarin for patients with antiphospholipid antibody syndrome), 2) it affects decisions regarding duration of anticoagulation, 3) thrombosis is in an unusual location (ie, hepatic vein thrombosis or noncirrhotic portal vein thrombosis), or 4) appropriate clinical history (ie, convincing family history, signs/symptoms of a myeloproliferative neoplasm or paroxysmal nocturnal hemoglobinuria).

Another controversy surrounds the use of TEG/ROTEM compared with standard laboratory assessment (PT/INR, activated partial thromboplastic time [aPTT]) in patients with liver disease. Should it replace the use of

INR/PT in all patients with advanced liver disease? We believe the answer is yes. The elevated PT and INR/PT that occurs in cirrhotic patients often occurs against the background of a normal or near-normal aPTT. Evaluating PT/INR in isolation does not take into account other issues such as thrombocytopenia and platelet dysfunction, although both of these issues are important in the patient with coagulopathy and advanced liver disease. TEG/ROTEM integrates these test results into one graphical representation. In patients with liver failure, PT results and INR calculation do not correlate well with more specific assessments of overall coagulation state using TEG. TEG provides the opportunity to determine a true coagulation profile that correlates well with the in vivo clinical presentation. Although TEG/ROTEM is not considered as standard of a technique as PT measurement and INR calculation, it has been shown to provide benefit when guiding procedures such as liver transplant.[1] It also has shown benefit when guiding the management of acute coagulopathy in critical acute settings such as the emergency room and military operations.[2-5] However, additional research is needed to more fully establish the role of TEG in the management of patients with advanced liver disease.

Much debate surrounds the implementation of anticoagulation therapy across all patients with portal vein thrombosis. As the thrombotic complications of advanced liver disease are increasingly recognized, the use of these agents in this setting is likely increasing. Given the limited clinical trials in this area, there are no consensus guidelines to provide recommendations. A nonblinded, single-center study by Villa and colleagues showed successful and safe prevention of portal vein thrombosis using prophylactic enoxaparin.[6] This study also demonstrated reduced bacterial translocation, a decrease in the incidence of hepatic decompensation, and improved survival. However, in the absence of well-designed clinical trials, other experts are of the opinion that the data are insufficient to justify widespread primary prophylaxis of portal vein thrombosis.[7] Instead, it may be considered on an individual case-by-case basis at the discretion of the treating physician.

With the availability of newer direct oral anticoagulants (DOACs; including apixaban, dabigatran, edoxaban, and rivaroxaban), there is a school of thought that these agents should completely replace the use of warfarin. Over the past several years, these newer anticoagulant agents have emerged as alternatives to warfarin for the prevention and treatment of venous thromboembolism and for the prevention of stroke in patients with atrial fibrillation. Based on the results of a number of randomized trials, these agents are now recommended as first-line treatment or as alternatives to warfarin for the management of atrial fibrillation and venous thromboembolism across multiple guidelines. However, the efficacy and safety of these drugs in the setting of liver disease have not been well studied, and none of the clinical practice guidelines offer direction regarding their use in patients with liver disease.[8] Indeed, these randomized trials largely excluded patients with liver disease. All of these agents undergo hepatic metabolism (to varying degrees), and therefore are subject to decreased liver function. In addition, the presence of hepatic coagulopathy may exacerbate the risk of bleeding associated with newer anticoagulant agents. In the wake of their approval for use, the hepatic safety of the newer anticoagulant agents has been followed and reported in clinical practice. It is clear that all of these agents are associated with elevations of transaminases. However, there remains no clear evidence that these agents result in hepatotoxicity, and a Canadian administrative database-linked cohort study recently found no significant difference in the rates of serious liver injury with DOACs compared with warfarin in patients with or without liver disease.[9]

The optimal management of patients with a baseline INR value higher than 2 who have an indication for therapeutic anticoagulation is unclear. Some advocate targeting an INR 1 unit above the patient's baseline INR value, but no higher than 3.5. However, evidence supporting this approach is lacking, and maintaining such a narrow therapeutic window in patients with advanced cirrhosis is often not feasible. Use of DOAC therapy to avoid the need for INR monitoring is appealing, but these agents have not been well-studied in patients with advanced cirrhosis. A tailored approach using individualized INR targets, reduced-dose DOAC therapy, or daily prophylactic dose low-molecular-weight heparin is often considered. Sometimes, no safe anticoagulant can be recommended.

Another controversy exists regarding the use of TPO-RAs in patients with low platelets (<50,000) as a prophylaxis prior to invasive procedures. Recently, this strategy was explored in ADAPT 1 and ADAPT 2, which were 2 identically designed, multicenter, randomized, double-blind, placebo-controlled studies.[10] A total of 435 patients with chronic liver disease were stratified according to baseline platelet count, with 184 in a high cohort (mean baseline platelet count of 40 to $<50 \times 10^9$/L) and 251 in a low cohort (mean baseline platelet count <40 $\times 10^9$/L). Patients in both cohorts were randomized in a 2-to-1 ratio to treatment with either avatrombopag or placebo. Avatrombopag was associated with a significant reduction in the primary endpoint, the need for platelet transfusion, or any rescue procedure for bleeding. Among patients with a high baseline platelet count in ADAPT 1 and ADAPT 2, the primary endpoint was met by 88% of those treated with avatrombopag, compared with 38% in

the placebo arm of ADAPT 1 and 33% in the placebo arm of ADAPT 2. A similar pattern was observed in patients with a low baseline platelet count. The primary endpoint was met by 66% of the treatment arm in ADAPT 1 and 69% of the treatment arm in ADAPT 2, vs 23% and 35%, respectively, of the placebo arms. Additionally, up to 93% of high-platelet patients and up to 69% of low-platelet patients who were treated with avatrombopag reached the secondary endpoint of a target platelet count of ≥50 × 10^9/L. In pooled analysis of the 2 trials, the most common (>5%) adverse events reported with avatrombopag were pyrexia, abdominal pain, nausea, and headache.

Lusutrombopag was evaluated in the L-PLUS 2 trial, a global, phase 3, randomized, double-blind, placebo-controlled study, for its ability to raise platelet counts in patients with chronic liver disease and thrombocytopenia who were undergoing invasive procedures.[11] A total of 215 patients were randomly assigned to treatment with lusutrombopag or placebo. The primary endpoint of avoidance of preprocedure platelet transfusion and avoidance of rescue therapy for bleeding was met by 64.8% of the lusutrombopag group compared with 29.0% of the placebo group (P<.0001). A key secondary endpoint, the number of days that platelet counts were ≥50 × 10^9/L throughout the study, was also significantly longer with lusutrombopag (without platelet transfusion) vs placebo (with platelet transfusion). The median duration of platelet counts of ≥50 × 10^9/L was 19.2 days with lusutrombopag vs 0.0 days with placebo (P=.0001). Most adverse events were mild or moderate in severity; headache was the only treatment-emergent adverse event reported in more than 5% of lusutrombopag-treated patients.

Although TPO-RAs have proven to be effective in raising platelet counts and reducing use of preoperative platelet transfusion, their effect in reducing procedure-related bleeding is less clear. No randomized trials have demonstrated reduction in the risk of procedural bleeding by raising the platelet count above a specific threshold. The safety profile of the 2 approved TPO-RAs is comparable to that of placebo, and these treatments can obviate the risks of platelet transfusion. Although these therapies are expensive, costing approximately $4,000 to $10,000 for a course of treatment (according to list price), the cost compares favorably with that of prophylactic platelet transfusion.[12]

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Notes