

Coagulation in Liver Disease: A Guide for the Clinician

PATRICK G. NORTHUP and STEPHEN H. CALDWELL

Division of Gastroenterology and Hepatology, Center for the Study of Coagulation in Liver Disease, University of Virginia, Charlottesville, Virginia

This article has an accompanying continuing medical education activity on page e67. Learning Objectives—At the end of this activity, the successful learner will be able to explain the current understanding of hemostasis in chronic liver disease, its laboratory abnormalities, and the strengths and weaknesses of current testing and treatment strategies.

Podcast interview: www.gastro.org/cghpodcast. Also available on iTunes.

The human hemostasis system is complex and poorly understood after decades of intense scientific study. Despite multiple defects in routine coagulation laboratory studies in patients with chronic liver disease, there is growing evidence that these patients are effectively “rebalanced” with regard to procoagulant and anticoagulant activity and that most of these patients remain in a tenuous but balanced state of hemostasis. A major difficulty in the assessment of these patients is that there are no established laboratory tests that accurately reflect the changes in both the procoagulant and anticoagulant systems; therefore, routine laboratory testing is misleading to the clinician and may prompt inappropriate or risky therapies with little real benefit to the patient. The international normalized ratio is an example of this type of misleading test. Although the international normalized ratio is inextricably linked to prognosis and severity of protein synthetic dysfunction in acute and chronic liver disease, it is a very poor marker for bleeding risk and should not be used in isolation for this purpose. Coagulation disorders are critical in the management of frequent clinical scenarios such as esophageal variceal bleeding, invasive and percutaneous procedures, portal vein thrombosis, venous thromboembolism, and acute liver failure. This article summarizes the pathophysiology of hemostasis in liver disease, describes the strengths and weaknesses of various laboratory tests in assessment of these patients, and outlines the optimal management of hemostasis for some common clinical scenarios. Further research is needed for proper understanding of hemostasis in liver disease to optimally and safely manage these complex patients.

Keywords: Coagulation; Liver; Varices; Bleeding Portal Vein Thrombosis; Acute Liver Failure.

Few aspects of liver disease have become associated with so much dogmatic practice, but so few data, as the management of liver-related acquired coagulation disorders. Changes in coagulation parameters have been a hallmark of advanced liver disease since laboratory testing became widely available in the mid-20th century; the prothrombin time (PT) and interna-

tional normalized ratio (INR) are now inextricably linked to prognosis and progression of liver disease. Mortality risk scores for cirrhosis such as the Child–Turcotte–Pugh and Model for End-Stage Liver Disease scores as well as the King’s College Criteria and factor V levels for acute liver failure (ALF) all have key components related to PT or INR. To a lesser extent, the blood platelet count is also commonly regarded as an indirect measure of portal hypertension related to splenic sequestration and loss of hepatic production of thrombopoietin because of liver tissue atrophy. Although it is clear that these measures are related to liver disease prognosis, ironically it is less clear how to use these tests to manage bleeding and clotting in the patient with acute and chronic liver disease. In this article, we will review essential and practical aspects of coagulation in liver disease. We will also discuss the limitations of laboratory tests in the investigation of bleeding or clotting risk in this patient population. Finally, we will address the prevalence and current clinical understanding of several common disease processes related to coagulation disorders in liver disease patients.

Physiology and Pathophysiology

Much of the understanding of the physiology of normal coagulation is derived from decades of research in patients with rare, usually congenital, clotting factor deficiencies. The prototypical disease in this category is hemophilia A, or congenital factor VIII deficiency; factor concentrates developed through research in this area led to a revolution in therapy for this population. However, the backwards engineering of the coagulation system through procoagulant pathways led to decades of narrow focused teaching that was subsequently propagated in medical schools. For example, the traditional understanding of an intrinsic pathway and extrinsic pathway of clotting that was taught to generations of students has led to an incomplete understanding in the mainstream medical community of the complexity and flexibility of the system involved in maintaining hemostasis in health and in disease. This has led

Abbreviations used in this paper: ALF, acute liver failure; EVBL, esophageal variceal band ligation; FFP, fresh frozen plasma; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PT, prothrombin time; PVT, portal vein thrombosis; VKA, vitamin K antagonist; VTE, venous thromboembolism; vWF, von Willebrand factor.

© 2013 by the AGA Institute

1542-3565/\$36.00

<http://dx.doi.org/10.1016/j.cgh.2013.02.026>

front-line providers to depend on outdated or irrelevant and potentially misleading tests in patients with liver disease.

Cell-based Model of Hemostasis

In the modern cell-based concept, hemostasis is viewed as a cellular process with the activated platelet as the primary effector and enabler of coagulation. The fundamental structure of a clot is a platelet plug restrained by a fibrin mesh formed by the conversion of fibrinogen to fibrin by the enzyme thrombin. The process involves 3 phases: (1) primary hemostasis or the initial plugging of the vascular breach by activated platelets; (2) coagulation, fibrin mesh construction, and clot fortification by the plasma procoagulant proteins; and once vascular repair is complete, (3) fibrinolysis or breakdown of the fibrin mesh by plasma anticoagulant proteins.¹ These processes are highly advanced and rapidly responsive to endothelial factors in the local environment and are typically triggered by exposure of tissue

factor to the luminal side of the vascular endothelium. Except in relatively rare cases of systemic coagulation such as disseminated intravascular coagulation, the local hemostatic mechanisms do not override the systemic balance of coagulation. This is why routinely available measures of coagulation are not effective at describing hemostasis at the site of injury. The lack of an established and valid systemic test to anticipate or diagnose coagulation changes in the local environment is a recurrent frustration for the clinician. Figure 1 graphically shows the phases of the hemostasis system and some of the laboratory testing available to describe each phase of the process.

Changes in Liver Disease

Liver disease is marked by changes in all phases of hemostasis caused by hepatic synthetic dysfunction and portal hypertension (with portosystemic shunting and endothelial

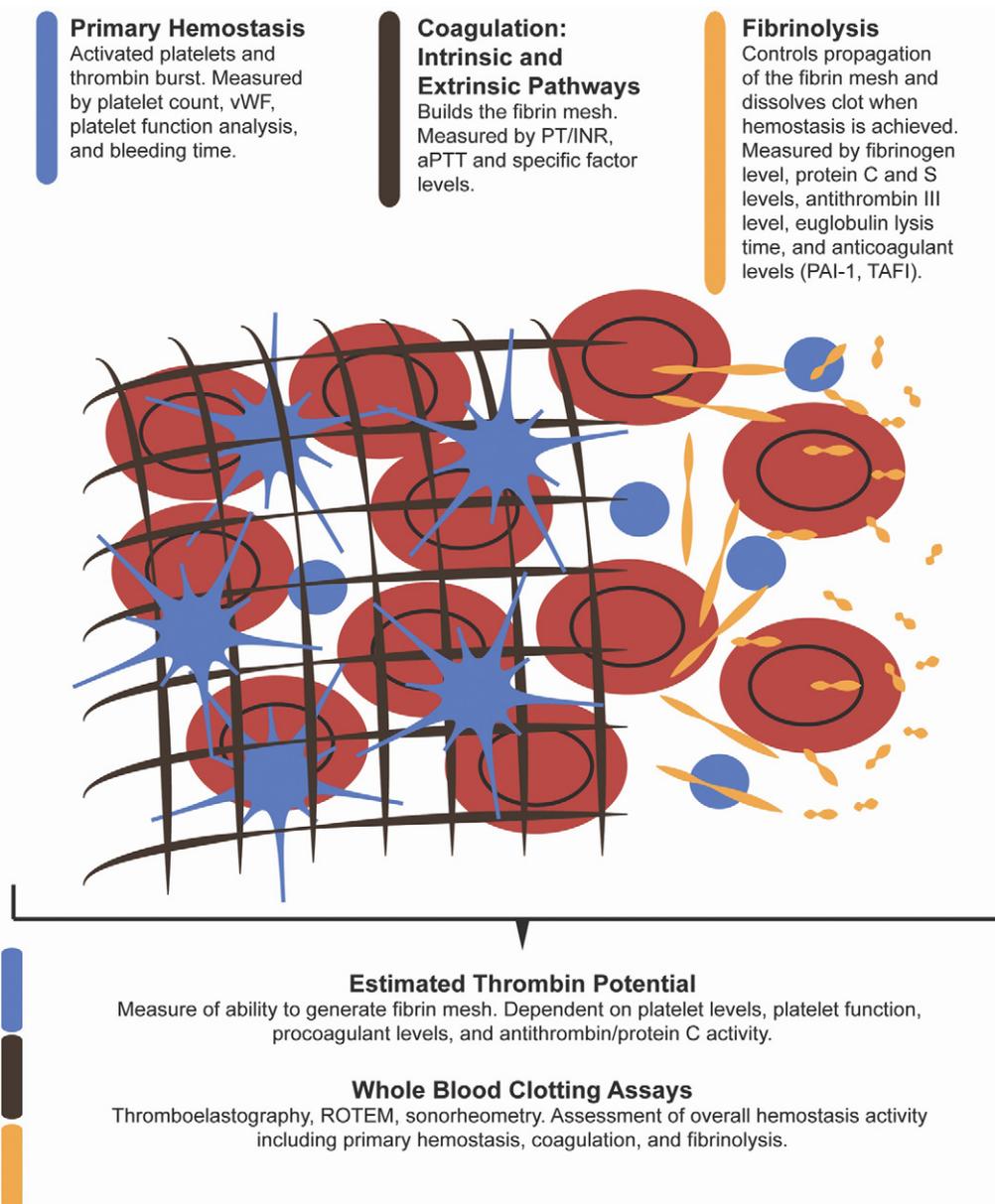


Figure 1. Phases of coagulation and laboratory testing available for analysis of each phase.

dysfunction). There are compensatory mechanisms that counterbalance these changes and lead to a “rebalancing”² of the coagulation system in patients with liver disease. For example, synthetic dysfunction and impaired protein production occur in both procoagulant and anticoagulant proteins, thereby counterbalancing each other.³ This compensatory rebalancing enables even the patient with advanced liver disease to uncommonly have spontaneous bleeding or clotting (without another specific trigger) and remain in a relatively balanced state of hemostasis.

Platelets

Primary hemostasis occurs when tissue factor is sensed on the luminal side of the vascular endothelium by platelets. Platelets respond to tissue factor by activating, developing pseudopods, and forming a platelet plug in the vascular breach. Activated platelets enable the rapid production of a fibrin mesh by exposing activated clotting factors on their surface and producing a “thrombin burst” through a positive feedback mechanism.⁴ The principal abnormality in chronic liver disease patients is a numeric decrease in the circulating platelet count. The etiology is generally thought to be multifactorial. There is undoubtedly pooling of platelets and sequestration in the spleen, and some authors have suggested a role of antiplatelet glycoprotein IIb-IIIa antibodies⁵ in cirrhosis patients, but an immunologic mechanism appears to be a minor contributor. There is also evidence for more rapid turnover and shorter half-life of platelets because of splenomegaly⁶ and decreased production because of lower levels of hepatic thrombopoietin.⁷ Although thrombopoietin levels recover after liver transplantation,⁸ the effect on pretransplant thrombocytopenia appears to be small.⁶

There is controversy regarding a qualitative defect in platelet function in liver disease. Platelet adherence to endothelial surfaces is mediated largely through von Willebrand factor (vWF), which is a large-molecular-weight glycoprotein that becomes active when cleaved into smaller subunits by the endothelial derived protease ADAMTS13. As a result of endothelial dysfunction, levels of vWF are elevated in proportion to the severity of liver disease.⁹ Under simulated flow conditions in vitro, platelets from cirrhosis patients have decreased adherence, but adherence increases in the presence of cirrhosis patients' plasma,¹⁰ an effect attributed to the excess vWF.¹¹ Despite these compensatory changes, the presence of a minimum number of platelets is required to fully support and initiate the thrombin burst and produce adequate end products for coagulation. Experiments with platelets from cirrhosis patients compared with healthy controls show that a level of around $50\text{--}60 \times 10^9/\text{L}$ is the relative floor for adequate thrombin generation, and levels above $100 \times 10^9/\text{L}$ show little extra benefit compared with controls.¹²

Coagulation Cascade

Liver disease, especially cirrhosis, is characterized by reduced synthesis of the procoagulant proteins II, VII, IX, X, as well as factor V and factor XI.¹³ These factor deficiencies directly affect the standard coagulation measures available in clinical laboratories, mainly the PT and its standardization, the INR, and to a lesser extent, the activated partial thromboplastin time. Therefore, the initial response of the practitioner is to assume a high risk of bleeding that is due to coagulation

protein deficiencies in this patient population. Research in hemostasis during the past decade has revealed this as a misconception.

Despite decreased levels of procoagulant factors and abnormal INR measurements, cirrhosis patients do not typically have spontaneous bleeding in sites where patients with congenital clotting factor deficiencies experience, such as hemarthroses, which argues that patients with liver disease have counterbalancing forces. In fact, there are strong in vitro data showing that in the presence of adequate platelet counts and thrombomodulin, an endothelial-derived cofactor in the anticoagulant system, cirrhosis patients have a normal capacity to generate thrombin^{12,14} and the fundamental building blocks of the fibrin mesh. The reason for this normal clotting potential is largely due to a decrease in synthesis of a potent anticoagulant protein C, coupled with increased endothelial-derived factor VIII.¹⁵ Therefore, the compensatory mechanisms in the patient with advanced liver disease effectively rebalance the hemostatic system.

Despite a rebalanced system, there are a variety of perturbations that can predispose an individual liver disease patient to bleeding or clotting. With the progression of disease, the activity of the procoagulant proteins drops to as low as 20%–46%.¹⁵ Although compensatory mechanisms are active, the capacity to adjust to insults to the system is diminished, and small perturbations can overcome the compensatory mechanisms. The rebalanced state can be likened to a tightrope crossing a gorge compared with a highway; there is much less room for upsets. Indeed, some patients with advanced liver disease have a loss of balance toward the clotting side, which is similar to patients with congenital protein C deficiency,¹⁵ and conversely, some patients are clearly more prone to bleeding. These tendencies are not static and may change with the clinical status of the patient, perhaps over hours during a hospital stay for decompensation. Acute events such as infection,¹⁶ variceal bleeding,¹⁷ and uremia¹⁸ lead to acute changes in coagulation in patients with liver disease, and these changes are at least partially reversible with proper treatment but are not well reflected in conventional tests such as the INR. The clinical challenge is determining which patients fall into which group before an event (bleeding or clotting) occurs.

Common Laboratory Tests: Strengths and Weaknesses

It is important to understand that the basic clinical laboratory tests available to the practitioner do not measure the compensatory mechanisms such as protein C activity or vWF levels. These tests only give information on small portions of the coagulation system that they were designed to analyze. This is the major difficulty with the clinical estimation of bleeding or clotting risk in this population, the lack of comprehensive testing to show the “big picture” in an individual patient. Table 1 shows the strengths and weaknesses of some laboratory tests available for measuring hemostasis and their applicability in liver disease patients.

The INR is possibly the most misunderstood laboratory test ordered in the evaluation of liver disease patients. The progression of protein synthetic dysfunction is inexorably linked with progression of liver disease and prognosis, whether in ALF or chronic liver disease. The inclusion of the INR (or PT) in multiple prognostic mortality equations for a broad array of

Table 1. Characteristics of Diagnostic Tests of Coagulation in Liver Disease: Their Weaknesses and Strengths

Test name	System analyzed	Strengths	Weaknesses
INR and PT	Classic procoagulant extrinsic pathway only	Widely available Inexpensive Quick Good correlation with severity of liver disease	High interlaboratory variability Narrow measure of procoagulant system only Not predictive of bleeding
Activated partial thromboplastin time	Classic procoagulant intrinsic pathway only	Widely available Inexpensive Quick Can detect congenital factor deficiencies	Usually does not reflect hepatic dysfunction Narrow measure of procoagulant system only Usually normal or nearly normal in liver disease
Platelet count	Platelet	Widely available Inexpensive Quick Reproducible and has some clinical correlate with bleeding at low levels ($<60 \times 10^9/L$)	Does not reflect platelet function Is not useful in predicting bleeding at higher levels
Platelet function assays	Platelets and primary hemostasis	Can give some evidence of generalized platelet function compared with normal	Most assays assume normal platelet counts and are not calibrated for thrombocytopenia Not universally available Not studied extensively in liver disease
Bleeding time	Mucosal and skin hemostasis	Can give a better view of whole system hemostasis	Generally does not predict procedural bleeding Not available in many centers Time-consuming to perform Patient discomfort
vWF complex levels	Primary hemostasis	Reflective of severity of liver disease and offers prognostic value in liver disease Low levels in liver disease might indicate need for platelet transfusion for prophylaxis	Generally not validated in predicting bleeding in cirrhosis Laboratory turnaround can be slow Complex relationship with ADAMTS13 and platelets not understood in cirrhosis
Fibrinogen	Fibrinolysis	Low levels suggestive of hyperfibrinolysis Levels >100 mg/dL suggest adequate fibrinogen for initiation of coagulation	Acute phase reactant Low levels are common in stable nonbleeding cirrhosis patients Not predictive of disseminated intravascular coagulation in cirrhosis
Factor levels	Procoagulant and anticoagulant pathways	Can give a relative sense for factor deficiencies on either procoagulant or anticoagulant system	Significant laboratory variation Factor levels are affected by acute clotting and other disease processes No clear relationship to bleeding or clotting risks
Euglobulin lysis time	Fibrinolysis	Validated measure of fibrinolysis Can be used as a measure of treatment efficacy in hyperfibrinolysis	Not widely available
Thromboelastography	Universal hemostasis	Used for decades for intraoperative transfusion guidance Can show defects in multiple components of hemostasis to guide therapies	Whole blood test requiring near immediate turnaround No standardization of most parameters Requires experience to interpret tracings Not validated in predicting bleeding or clotting in nonsurgical patients May be insensitive in the hypercoagulation population

Table 1. Continued

Test name	System analyzed	Strengths	Weaknesses
Sonorheometry	Universal hemostasis	Can show defects in multiple components of hemostasis to guide therapies May be more sensitive than thromboelastography in the hypercoagulation population More automated and less technically difficult than thromboelastography	Experimental use only Not clinically validated
Endogenous thrombin potential	Procoagulant and anticoagulant pathways	Gives better view of the balance between procoagulation and anticoagulation	Experimental only Addition of thrombomodulin not standardized Dependent on platelet count
Procoagulant microparticle assays	Procoagulant pathway	May describe tendency for hypercoagulation	Highly experimental and not validated

liver diseases is evidence of the INR's close relationship to hepatic synthetic dysfunction. Despite this, there are so many problems with INR as a measure of hemostasis in cirrhosis that its position as an indicator of plasma transfusion is inexplicable, and its use in guidelines at specific values amounts to something of a religious belief.

The INR was originally developed in the early 1980s for standardization of therapeutic anticoagulation with vitamin K antagonists (VKAs), and the calibration of the test is computed from healthy volunteers. The INR has been successful in improving the management of therapeutic anticoagulation in this role. In fact, the INR is simply a reflection of the PT ratio compared with controls by using a correction factor that is based on the specific thromboplastin used in the PT measurement. However, the common INR is not calibrated for use in liver disease, especially cirrhosis patients. This is most evident in the remarkably high interlaboratory variability in liver disease patients, depending on which thromboplastin reagent is purchased for the assay.^{19,20} Some authors have argued for a "liver calibrated" INR²¹ that uses cirrhosis patients as controls and a standard thromboplastin reagent, but the potential economics of this recalibration and logistical difficulties with its widespread adoption make the INR(liver) more of a theoretical option than a reality and does not resolve the limitations of the test as a measure of hemostasis.

Risk Assessment for Procedures

A frequent clinical need is predicting bleeding during or after procedures. The INR gives a very narrow view of a single aspect of hemostasis in cirrhosis, and one would predict that it would not offer much use in the prediction of bleeding in liver disease patients. Despite this, the INR is currently in widespread use for this purpose by proceduralists and surgeons, perhaps because of its availability, the lack of an established alternative, and a misunderstanding of its meaning. Interestingly, there are numerous published studies affirming the lack of utility of INR in accurately predicting procedural bleeding in liver disease patients in a very broad array of procedures including percutaneous,²² laparoscopic,^{23,24} and transjugular liver biopsy,^{25,26} therapeutic paracentesis,²⁷ colonoscopy with polypectomy,²⁸ percutaneous endoscopic gastrostomy,²⁹ dental extractions,³⁰ bronchoscopy, transjugular and percutaneous

renal biopsy, central venous catheter placement, arteriography,²⁵ and coronary artery catheterization.³¹ It is also documented that when clinicians attempt to "correct" the INR by using fresh frozen plasma (FFP) before procedures, the clinicians use inadequate doses of FFP and rarely achieve the INR goals with transfusion alone.³²

In recent years, some professional societies have recognized the weakness of the INR as a measure of bleeding risk. Specifically, the American Association for the Study of Liver Diseases practice guideline for the performance of liver biopsy³³ states that there is no specific PT-INR level that clearly predicts bleeding during or after biopsy. In contrast, the Society of Interventional Radiology Standards of Practice Document for management of coagulation status before image-guided interventions³⁴ acknowledges that moderately elevated coagulation times should not be assumed to represent increased bleeding risk but recommends correction with FFP (or vitamin K) to an INR of 2.0 for low-risk procedures and 1.5 for moderate-risk or higher-risk procedures. Confusingly, this recommendation does not differentiate between liver disease patients and therapeutically anticoagulated patients with VKAs and is based on only a Delphi consensus recommendation of a committee of interventional radiologists.

Other Measures of Bleeding Risk

There are other common and uncommon laboratory tests of the hemostatic system in patients with liver disease that can be used for bleeding and clotting prediction. The blood platelet count is an effective screening tool for detecting high-risk bleeding patients only at the extreme levels. There is physiological evidence that a peripheral platelet count of $50-60 \times 10^9/L$ is adequate to promote the thrombin burst and kindle the coagulation cascade, whereas $100 \times 10^9/L$ is a ceiling above which little more thrombin potential is extracted. Retrospective clinical studies have suggested that there is a relatively higher risk for bleeding after percutaneous liver biopsy at platelet counts below the $60 \times 10^9/L$ level, although it should be noted that most bleeding cases in this study occurred at relatively high platelet counts.^{35,36} There are commercial platelet function assays such as the platelet function analyzer 100,³⁷ but their clinical availability is limited, and their applicability to liver disease patients is currently unknown because most of these

assays depend on normal platelet counts to give accurate platelet function estimates. Because of the significantly elevated vWF factor levels in cirrhosis, some have advocated the use of vWF-factor VIII complex levels as markers for bleeding risk in cirrhosis patients. The vWF levels have been implicated as a marker of endothelial dysfunction in cirrhosis patients,³⁸ and vWF levels have been independently linked to portal hypertension complications⁹ but not specifically to bleeding alone.

In regard to the fibrinolytic pathway, currently available diagnostic testing is inadequate or unavailable to the clinician. Bleeding time has historically been a measure of bleeding risk in cirrhosis patients and has been linked to hyperfibrinolysis, but this test has fallen out of favor because of its lack of sensitivity in predicting bleeding,³⁹ its limited utility relative to laboratory time consumption, patient discomfort, and blood exposure to laboratory personnel associated with the test. Fibrinogen levels are an indirect marker of clot-making capacity or rapid clot breakdown. However, reports of fibrinogen levels in cirrhosis patients are variable,⁴⁰ and there appears to be no clear relationship to fibrinogen levels and bleeding in liver disease except in patients with a clear disseminated intravascular coagulation syndrome, usually in the setting of multisystem organ failure or sepsis or less commonly during the anhepatic and post-reperfusion state during liver transplant operations.⁴¹ Fibrinogen is also an acute phase reactant, and levels can fluctuate significantly. Supplementation (usually through cryoprecipitate) is an accepted practice in controlling bleeding that is due to massive hemorrhage or trauma,⁴² but it has not been studied for bleeding or prophylaxis in nontransplant liver disease. The euglobulin lysis time has been validated as a measure of hyperfibrinolysis in hospitalized decompensated cirrhosis patients⁴³ and correlates with mucocutaneous bleeding, but the test is not readily available in most clinical laboratories.

The above tests evaluate narrow aspects of the hemostatic system but suffer in applicability for that very reason. They do not measure the capacity of the system to accommodate changes and adapt by using other unmeasured pathways. Thromboelastography has been used for many years as a whole blood measure of the clotting system, mainly in the operating room during surgeries involving massive transfusion or bleeding⁴⁴ or in cardiovascular disease.⁴⁵ By using whole blood, these devices measure clot stiffness from the point of primary hemostasis through stabilization through fibrinolysis and produce a graphical representation of the process.⁴⁶ A similar device called rotational thromboelastometry is also in use. Because the measurements are made continuously during clot formation and breakdown and because whole blood is used, theoretically all components of the hemostatic system are analyzed by these devices including platelet function, hypercoagulability, and fibrinolysis. Although used frequently in the operative setting, especially in Europe, direct applicability to bleeding risk and assessment of clinical hypercoagulability syndromes in liver disease patients are preliminary and have not been prospectively validated.⁴⁷ Newer technology using ultrasonic pulses to assess clot strength that may be more sensitive at the extremes of clot stiffness are in development but not available for clinical use.⁴⁸ Weaknesses of all currently available whole blood testing devices are the need for fresh whole blood samples (usually less than 4 hours from phlebotomy), a time-consuming and technically rigorous operation, and a certain amount of expertise in subjective graphical output interpretation required by the cli-

nician. There are a number of other experimental methods under investigation as measures of hemostasis in liver disease. Endogenous thrombin potential,¹⁴ factor VIII/protein C activity⁴⁹ ratio, and plasma microparticle activity⁵⁰ have all been critically important in experimental and research settings to help elucidate bleeding and clotting risks, but none have shown clinical utility at this point or are still in investigational stages.

Common Clinical Issues in Coagulation

Variceal Bleeding

Variceal bleeding is one of the most common bleeding events experienced by patients with advanced liver disease. Patients with cirrhosis will experience the development of varices at a rate of about 8% per year after the onset of cirrhosis.⁵¹ Once formed, risk factors for bleeding are predominantly related to hemodynamic and mechanical parameters such as hepatic vein-portal pressure gradient,⁵² varix size, their appearance (red marks and purple color), and the severity of the underlying liver disease.⁵³ Aside from the relationship to severity, there have been few data to support the notion that coagulopathy is directly related to variceal bleeding risk, although increased markers of fibrinolysis were predictive of eventual variceal bleeding in one study.⁵⁴ However, this relationship may reflect worsening portal pressure rather than the direct effect of fibrinolysis. In addition, the existence of the platelet plug (nipple sign) as a high-risk marker for variceal bleeding indicates at least some transient role of primary hemostasis in acute bleeding.

Despite specific practice guidelines on management of esophageal varices by the American Association for the Study of Liver Diseases, the American College of Gastroenterology,⁵⁵ and the American Society for Gastrointestinal Endoscopy,⁵⁶ there are no specific recommendations on coagulation parameters for prophylactic esophageal variceal band ligation (EVBL). Because there is little evidence that coagulation disorders increase the risk for post-EVBL bleeding⁵⁷ and no evidence supporting prophylactic transfusion before EVBL, this practice cannot be endorsed as routine. In those with coagulation disorders that prohibit the practitioner from safely performing EVBL, then nonselective β -blockers alone would be the preferred therapy for primary bleeding prophylaxis.

For acute variceal bleeding, there is little consensus regarding coagulation management during the immediate bleeding episode. Blood resuscitation should aim for a target hemoglobin in the 7–8 g/dL range.⁵⁸ Overtransfusion of red cells or large volumes of plasma should be avoided because of resultant increases in portal pressures⁵⁹ and increased rebleeding rates.⁶⁰ A recent large randomized controlled trial of transfusion strategies in acute gastrointestinal bleeding supports this notion and suggests a hemoglobin target of 7 g/dL.⁶¹ Optimal platelet counts remain uncertain, although on the basis of adequate thrombin production, levels exceeding $56 \times 10^9/L$ are recommended. A fibrinogen level above 100–150 mg/dL is sometimes recommended by using cryoprecipitate transfusion but remains to be adequately tested in clinical trials, and “adequate” levels are uncertain. FFP is problematic because of the large volume needed to actually replenish coagulation factors⁶² (usually 20–40 mL/kg). This dose usually requires several liters of FFP to “correct” the INR and thus may worsen portal pressure, precipitate anasarca, and expose the patient to events such as transfusion-related acute lung injury, cardiogenic pulmonary

edema, and iatrogenic increases in portal pressures raising re-bleeding risk. Because of the negative clinical trial data and high expense, recombinant activated factor VII cannot be recommended for general use, although its role as a true rescue factor during active bleeding with obscured endoscopic fields remains to be adequately studied. Other factor concentrates and specialty products are under development but not studied in this situation.

Other Invasive Procedures

There are no good measures of bleeding risk before invasive procedures that are currently available to the practicing clinician, and practice guidelines vary wildly in recommendations that are based on the issuing authority. One practical recommendation that can be made is that truly elective procedures should be delayed during acute events that might upset the rebalanced hemostatic system in cirrhosis patients: acute infection, severe acute alcoholic hepatitis, and uremia. Decisions to proceed with elective or semielective procedures should not be solely based on the INR and platelet counts but on the severity of comorbidities of the patient, the urgency of the procedure, the accessibility of the procedural site to mechanical hemostasis maneuvers, and the ability to detect bleeding at the site early in the hemorrhage.

There are very few randomized, double-blind controlled clinical trials assessing the effectiveness of prophylactic transfusion before low-risk invasive procedures such as endoscopic examinations, superficial biopsies, or paracenteses. As an indication of the lack of adequate study in this field, we are aware of only one that was a controlled trial investigating bleeding after dental extractions³⁰ that randomized patients to prophylactic FFP transfusion vs intranasal desmopressin. The researchers found that desmopressin was as effective as transfusion, more convenient, better tolerated, and less expensive. Acknowledging this important study, there is little theoretical, laboratory, or clinical benefit to prophylactic FFP transfusion, even though this is the most commonly performed transfusion practice before procedures.²⁷ Despite this, if the proceduralist decides on prophylactic transfusion, in cirrhosis patients the INR should not be used as a sole measure of bleeding risk, and physiologically it would be more appropriate to achieve a platelet count greater than $50-60 \times 10^9/L$ for high-risk procedures by using platelet transfusions.

Although Model for End-Stage Liver Disease is a validated tool for predicting surgical mortality in cirrhosis patients,⁶³ coagulation and bleeding complications are rare causes of mortality in the cirrhosis patient undergoing elective surgery. For nonhepatic surgical procedures, there are sparse data, and much of the transfusion practice is based on nonvalidated protocol-driven anesthesiology recommendations or on surgical assessment of bleeding in the field. Using thromboelastography in the operating room could be helpful in targeting transfusion practice, but wider training and experience are needed for this to become routine.⁶⁴ Surgical teams should be aware that persistent postoperative wound, mucosal, or puncture site bleeding could be a sign of hyperfibrinolysis, which warrants more specific therapy.

Portal Vein Thrombosis

Portal vein thrombosis (PVT) is a common occurrence in patients with cirrhosis, with a prevalence of at least 11%⁶⁵ in

patients with well-defined cirrhosis and as high as 36% at the time of autopsy.⁶⁶ There is also mounting evidence that the development of occlusive PVT is a milestone in the progression of liver disease and portends worsening portal hypertension and increased risk of death. In the setting of acute PVT without underlying liver disease, the presentation may be more ominous or life-threatening, and aggressive anticoagulation should be initiated. In patients with chronic liver disease, PVT is typically a more chronic or subacute development and is frequently accompanied by no symptoms or by only a worsening of the complications of portal hypertension.

There is mounting evidence that treatment or prevention of PVT with low-molecular-weight heparin (LMWH) in selected cirrhosis patients can avert intrahepatic thrombotic disease and recannulate or resorb early clots.⁶⁷ A preemptive treatment strategy in cirrhosis patients at high risk for PVT was evaluated in a randomized nonblinded clinical trial.⁶⁸ In this trial, during a period of 48 weeks, the LMWH treatment arm showed a significant benefit in the prevention of PVT formation, a lower chance of first hepatic decompensation, and better survival.

These thought-provoking data raise interest in further study of anticoagulation in this patient population as a means of preventing progression of stable cirrhosis to the decompensated state. More comprehensive studies to address the efficacy and the risk-benefit of this approach are needed. Although hemostatic mechanisms have not clearly been associated with variceal or other portal hypertensive bleeding, these are obviously a concern, and varices should be resolved before undertaking anticoagulation. The clinician should be clear on the criteria used in these trials. In general, these studies have focused on subacute or acute thrombus rather than chronic PVT with cavernous transformation. The use of LMWH has been common in these trials, although specific dosing has not been extensively studied, and the patients should have adequate renal function to tolerate LMWH. VKAs have been studied in this population and have a narrow therapeutic window with high complication rates.⁶⁹ Whether prophylactic or therapeutic, the practice of treating PVT is still a developing standard, and further data are needed to prove efficacy and safety.

Hypercoagulation and Venous Thromboembolism in Cirrhosis

Because of the coagulation imbalance in some patients with cirrhosis due to relative protein C deficiency and factor VIII excess,⁴⁹ there are patients with chronic liver disease who are prone to hypercoagulation. Although many of these patients remain asymptomatic or have a higher risk of PVT, there are multiple studies confirming the risk of peripheral thromboembolic disease such as deep vein thrombosis and pulmonary embolism in cirrhosis patients,^{70,71} despite abnormal INR values and thrombocytopenia. Commonly available clinical variables that can predict the increased risk for venous thromboembolism (VTE) are not well elucidated, although a low protein state as reflected by a serum albumin less than 2.8 g/dL is a rough indicator. Preliminary reports indicate that standard pharmacologic prophylaxis is safe,⁷² but effectiveness and the proper agents remain to be proven. The clinician should consider the risks and benefits of VTE prophylaxis in each individual patient, but with the current lack of definitive treatment data and a significant defined incidence of in-hospital VTE, it would seem reasonable to offer standard pharmacologic VTE

Table 2. Opportunities and Pitfalls in Management of Some Common Clinical Issues Related to Coagulation in Liver Disease

Clinical issue	Successful coagulation management opportunity	Potential pitfalls
Bleeding esophageal varices	Rapid endoscopic and medical therapy should be applied Transfuse platelet concentrates with target of at least $56 \times 10^9/L$ Maintain fibrinogen >100 mg/dL with cryoprecipitate Goal should be to resuscitate as needed but avoid increase in portal pressure	Avoid overtransfusion with packed red blood cells, aim for target hemoglobin or 7 g/dL Avoid use of empiric FFP unless clear indications are evident
Performance of invasive procedures	Weigh the risks of severe procedural bleeding (and the ability to stop it) against the need for prophylaxis If high-risk procedure, transfuse prophylactic platelets to a target of at least $50\text{--}60 \times 10^9/L$ or closer to $100 \times 10^9/L$ for very high risk If postprocedural bleeding occurs in mucosal sites or from puncture wounds, consider hyperfibrinolysis Treat underlying disorders aggressively before elective procedures (infection, renal failure, etc) Intranasal DDAVP may be an effective and economical alternative prophylactic measure in procedures such as dental extractions	Do not use a moderately elevated INR (<3) as a measure of procedural bleeding risk Avoid using FFP for prophylaxis, but if used, recall that adequate dosing to replace factors is $20\text{--}40$ mL/kg rFVIIa should be avoided for prophylaxis in all but the highest-risk procedures
PVT	Acute or subacute PVT can be treated with therapeutic anticoagulation (LMWH) and may prolong survival in these patients Esophageal varices should be treated aggressively endoscopically before anticoagulation	Currently available VKAs have a very narrow therapeutic window in cirrhosis patients and are especially problematic in patients with baseline elevated INR Patients with chronic PVT and cavernous transformation are less likely to benefit from anticoagulation Premature discontinuation of anticoagulation (before transplant) is likely to result in thrombus recurrence
Deep vein thrombosis or pulmonary embolus	Consider medical prophylaxis in all hospitalized cirrhosis patients as with any medical inpatient Medical therapy for acute VTE should be with LMWH in therapeutic doses similar to PVT treatment unless contraindicated	Do not assume the hospitalized cirrhosis patient is "auto-anticoagulated" because the INR is elevated Presence of nonbleeding esophageal varices should not preclude VTE prophylaxis
ALF	Despite highly abnormal traditional coagulation indexes, most ALF patients have reached a whole body hemostatic balance A single dose of rFVIIa ($40 \mu\text{g}/\text{kg}$) can facilitate performance of intracranial pressure monitor placement in ALF patients	Do not use prophylactic transfusion of FFP or platelets in ALF without clinically evident bleeding Do not use continuous infusions of rFVIIa in ALF patients because of the potential for thrombotic complications and high cost

rFVIIa, recombinant activated factor VII.

prophylaxis in hospitalized cirrhosis patients unless an obvious contraindication is present independent of standard coagulation laboratory values. Treatment for new diagnoses of VTE should essentially follow the same protocol as for PVT, except if a delay in treatment is expected because of high-risk esophageal varices eradication, a temporary inferior vena cava filter may be considered, although their use is controversial in many situations.

Acute Liver Failure

ALF is an uncommon but catastrophic destruction of liver tissue in a patient with previously normal liver function. Profound hepatic synthetic dysfunction is the hallmark of the disorder, with resulting metabolic disarray, highly abnormal INR and typical laboratory markers of coagulation, alterations in immunologic function, and ultimately cerebral edema. Despite the clear relationship of the prolonged PT/INR to poor prognosis and eventual death or requirement for liver transplantation, the syndrome is

rarely accompanied by significant clinical bleeding. Because of the relative rarity of the syndrome and the typical acute presentation, ALF is difficult to study, and only recently have large multicenter trials been feasible.⁷³ Recent work that used data from the U.S. ALF Study Group has revealed that despite the profound elevation in INR in most patients with ALF, there appear to be minimal global effects on hemostasis as measured by whole blood clotting analyses⁷⁴ and a general hypofibrinolytic state that is due to decreased plasminogen and elevated plasminogen activator type 1.⁷⁵ This results in the clinical state of relative hemostasis despite great disturbances in INR. This finding solidifies the recommendation that prophylactic correction of the coagulopathy in ALF patients should not be attempted without clear clinical bleeding. For high-risk invasive procedures with potential catastrophic bleeding consequences such as intracranial pressure monitor placement, a single dose of recombinant activated factor VII given at $40 \mu\text{g}/\text{kg}$ within minutes of the procedures can correct the INR to near normal levels.⁷⁶ This practice should be used only for the highest-

risk procedures, and continuous factor infusions should not be used because of the risk for thrombotic complications related to this agent. Table 2 summarizes some management issues related to coagulation in specific clinical liver diseases.

Summary and Future Directions

Despite intense study of the hemostatic system in congenital diseases with factor deficiencies, medical knowledge has only recently begun to expand in the area of hemostasis in liver disease. In this population, the traditionally used measures of coagulopathy are insufficient to describe the complex changes in primary hemostasis and platelet function, coagulation, and fibrinolysis. The clinician caring for patients with advanced liver disease suffers from a lack of accurate, reliable, and clinically available testing methods to properly assess the true state of hemostasis because some patients with chronic liver disease are predisposed for bleeding, some for hypercoagulation, and some in a tenuous but stable balance. More translational and clinical research is clearly needed to optimize the care for this growing population of patients with liver disease.

References

1. Tripodi A, Primignani M, Mannucci PM. Abnormalities of hemostasis and bleeding in chronic liver disease: the paradigm is challenged. *Intern Emerg Med* 2010;5:7–12.
2. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011;365:147–156.
3. De Caterina M, Tarantino G, Farina C, et al. Haemostasis unbalance in Pugh-scored liver cirrhosis: characteristic changes of plasma levels of protein C versus protein S. *Haemostasis* 1993;23:229–235.
4. Tripodi A. Hemostasis in chronic liver disease. *J Thromb Haemost* 2006;4:2064–2065.
5. Kajihara M, Kato S, Okazaki Y, et al. A role of autoantibody-mediated platelet destruction in thrombocytopenia in patients with cirrhosis. *Hepatology* 2003;37:1267–1276.
6. Kajihara M, Okazaki Y, Kato S, et al. Evaluation of platelet kinetics in patients with liver cirrhosis: similarity to idiopathic thrombocytopenic purpura. *J Gastroenterol Hepatol* 2007;22:112–118.
7. Pradella P, Bonetto S, Turchetto S, et al. Platelet production and destruction in liver cirrhosis. *J Hepatol* 2011;54:894–900.
8. Martin TG 3rd, Somberg KA, Meng YG, et al. Thrombopoietin levels in patients with cirrhosis before and after orthotopic liver transplantation. *Ann Intern Med* 1997;127:285–288.
9. La Mura V, Reverter JC, Flores-Arroyo A, et al. Von Willebrand factor levels predict clinical outcome in patients with cirrhosis and portal hypertension. *Gut* 2011;60:1133–1138.
10. Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology* 2006;44:53–61.
11. Lisman T, Adelmeijer J, de Groot PG, et al. No evidence for an intrinsic platelet defect in patients with liver cirrhosis: studies under flow conditions. *J Thromb Haemost* 2006;4:2070–2072.
12. Tripodi A, Primignani M, Chantarangkul V, et al. Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology* 2006;44:440–445.
13. Sleisenger MH, Feldman M, Friedman LS, et al. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. Philadelphia: Saunders/Elsevier, 2010.
14. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 2005;41:553–558.
15. Tripodi A, Primignani M, Chantarangkul V, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology* 2009;137:2105–2111.
16. Ferro D, Basili S, Lattuada A, et al. Systemic clotting activation by low-grade endotoxaemia in liver cirrhosis: a potential role for endothelial procoagulant activation. *Ital J Gastroenterol Hepatol* 1997;29:434–440.
17. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998;27:1207–1212.
18. Sagripanti A, Cupisti A, Baicchi U, et al. Plasma parameters of the prothrombotic state in chronic uremia. *Nephron* 1993;63:273–278.
19. Trotter JF, Brimhall B, Arjal R, et al. Specific laboratory methodologies achieve higher model for endstage liver disease (MELD) scores for patients listed for liver transplantation. *Liver Transpl* 2004;10:995–1000.
20. Lisman T, van Leeuwen Y, Adelmeijer J, et al. Interlaboratory variability in assessment of the model of end-stage liver disease score. *Liver Int* 2008;28:1344–1351.
21. Tripodi A, Chantarangkul V, Primignani M, et al. The international normalized ratio calibrated for cirrhosis (INR(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. *Hepatology* 2007;46:520–527.
22. Gilmore IT, Burroughs A, Murray-Lyon IM, et al. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut* 1995;36:437–441.
23. Ewe K. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. *Dig Dis Sci* 1981;26:388–393.
24. Denzer U, Helmreich-Becker I, Galle PR, et al. Liver assessment and biopsy in patients with marked coagulopathy: value of mini-laparoscopy and control of bleeding. *Am J Gastroenterol* 2003;98:893–900.
25. Segal JB, Dzik WH, Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005;45:1413–1425.
26. Bruzzi JF, O'Connell MJ, Thakore H, et al. Transjugular liver biopsy: assessment of safety and efficacy of the Quick-Core biopsy needle. *Abdom Imaging* 2002;27:711–715.
27. Grabau CM, Crago SF, Hoff LK, et al. Performance standards for therapeutic abdominal paracentesis. *Hepatology* 2004;40:484–488.
28. Jeon JW, Shin HP, Lee JI, et al. The risk of postpolypectomy bleeding during colonoscopy in patients with early liver cirrhosis. *Surg Endosc* 2012;26:3258–3263.
29. Baltz JG, Argo CK, Al-Osaimi AM, et al. Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series. *Gastrointest Endosc* 2010;72:1072–1075.
30. Stanca CM, Montazem AH, Lawal A, et al. Intranasal desmopressin versus blood transfusion in cirrhotic patients with coagulopathy undergoing dental extraction: a randomized controlled trial. *J Oral Maxillofac Surg* 2010;68:138–143.
31. Townsend JC, Heard R, Powers ER, et al. Usefulness of international normalized ratio to predict bleeding complications in patients with end-stage liver disease who undergo cardiac catheterization. *Am J Cardiol* 2012;110:1062–1065.
32. Youssef WI, Salazar F, Dasarathy S, et al. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. *Am J Gastroenterol* 2003;98:1391–1394.
33. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. *Hepatology* 2009;49:1017–1044.
34. Patel IJ, Davidson JC, Nikolic B, et al. Consensus guidelines for

- periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol* 2012;23:727–736.
35. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol* 2010;8:877–883.
 36. Caldwell S, Northup PG. Bleeding complication with liver biopsy: is it predictable? *Clin Gastroenterol Hepatol* 2010;8:826–829.
 37. Chang YW, Liao CH, Day YJ. Platelet function analyzer (PFA-100) offers higher sensitivity and specificity than thromboelastography (TEG) in detection of platelet dysfunction. *Acta Anaesthesiol Taiwan* 2009;47:110–117.
 38. Ferro D, Quintarelli C, Lattuada A, et al. High plasma levels of von Willebrand factor as a marker of endothelial perturbation in cirrhosis: relationship to endotoxemia. *Hepatology* 1996;23:1377–1383.
 39. Basili S, Ferro D, Leo R, et al. Bleeding time does not predict gastrointestinal bleeding in patients with cirrhosis: the CALC group—Coagulation Abnormalities in Liver Cirrhosis. *J Hepatol* 1996;24:574–580.
 40. Arif S, Khan AS, Khan AR. Changes in fibrinogen level in liver cirrhosis. *J Ayub Med Coll Abbottabad* 2002;14:19–21.
 41. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. *Anesth Analg* 1985;64:888–896.
 42. Ranucci M, Solomon C. Supplementation of fibrinogen in acquired bleeding disorders: experience, evidence, guidelines, and licences. *Br J Anaesth* 2012;109:135–137.
 43. Gunawan B, Runyon B. The efficacy and safety of epsilon-aminocaproic acid treatment in patients with cirrhosis and hyperfibrinolysis. *Aliment Pharmacol Ther* 2006;23:115–120.
 44. Wang JS, Lin CY, Hung WT, et al. Thromboelastogram fails to predict postoperative hemorrhage in cardiac patients. *Ann Thorac Surg* 1992;53:435–439.
 45. De Matteis F, Barbano G. The thromboelastogram in acute myocardial infarction not treated with anticoagulants. *Panminerva Med* 1961;3:124–126.
 46. Salooja N, Perry DJ. Thrombelastography. *Blood Coagul Fibrinolysis* 2001;12:327–337.
 47. Tripodi A, Primignani M, Chantarangkul V, et al. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. *Thromb Res* 2009;124:132–136.
 48. Viola F, Kramer MD, Lawrence MB, et al. Sonorheometry: a noncontact method for the dynamic assessment of thrombosis. *Ann Biomed Eng* 2004;32:696–705.
 49. Tripodi A, Primignani M, Lemma L, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. *Hepatology* 2010;52:249–255.
 50. Rautou PE, Bresson J, Sainte-Marie Y, et al. Abnormal plasma microparticles impair vasoconstrictor responses in patients with cirrhosis. *Gastroenterology* 2012;143:166–176.
 51. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254–2261.
 52. Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985;5:419–424.
 53. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. *N Engl J Med* 1988;319:983–989.
 54. Violi F, Leo R, Basili S, et al. Association between prolonged bleeding time and gastrointestinal hemorrhage in 102 patients with liver cirrhosis: results of a retrospective study. *Haematologica* 1994;79:61–65.
 55. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922–938.
 56. Qureshi W, Adler DG, Davila R, et al. ASGE guideline: the role of endoscopy in the management of variceal hemorrhage, updated July 2005. *Gastrointest Endosc* 2005;62:651–655.
 57. Vieira da Rocha EC, D'Amico EA, Caldwell SH, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. *Clin Gastroenterol Hepatol* 2009;7:988–993.
 58. de Franchis R, Baveno V faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010;53:762–768.
 59. Kravetz D, Sikuler E, Groszmann RJ. Splanchnic and systemic hemodynamics in portal hypertensive rats during hemorrhage and blood volume restitution. *Gastroenterology* 1986;90:1232–1240.
 60. Castañeda B, Morales J, Lionetti R, et al. Effects of blood volume restitution following a portal hypertensive-related bleeding in anesthetized cirrhotic rats. *Hepatology* 2001;33:821–825.
 61. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368:11–21.
 62. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. *Am J Clin Pathol* 2006;126:133–139.
 63. Northup PG, Wanamaker RC, Lee VD, et al. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg* 2005;242:244–251.
 64. Chitlur M, Sorensen B, Rivard GE, et al. Standardization of thromboelastography: a report from the TEG-ROTEM working group. *Haemophilia* 2011;17:532–537.
 65. Amitrano L, Guardascione MA, Brancaccio V, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. *J Hepatol* 2004;40:736–741.
 66. Wanless IR, Wong F, Blendis LM, et al. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. *Hepatology* 1995;21:1238–1247.
 67. Senzolo M, Sartori TM, Rossetto V, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int* 2012;32:919–927.
 68. Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012;143:1253–1260.
 69. García-Fuster MJ, Abdilla N, Fabiá MJ, et al. [Venous thromboembolism and liver cirrhosis]. *Rev Esp Enferm Dig* 2008;100:259–262.
 70. Northup PG, McMahon MM, Ruhl AP, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol* 2006;101:1524–1528, quiz 1680.
 71. Sogaard KK, Horváth-Puhó E, Grønbaek H, et al. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol* 2009;104:96–101.
 72. Intagliata N, Henry Z, Shah NL, et al. Prophylactic anticoagulation for deep venous thrombosis in hospitalized cirrhosis patients is safe and does not lead to increased bleeding events. *Hepatology* 2011;54:1253A.

73. Lee WM. Acute liver failure in the United States. *Semin Liver Dis* 2003;23:217–226.
74. Stravitz RT, Lisman T, Luketic VA, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *J Hepatol* 2012;56:129–136.
75. Lisman T, Bakhtiari K, Adelmeijer J, et al. Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure. *J Thromb Haemost* 2012;10:1312–1319.
76. Shami VM, Caldwell SH, Hespenheide EE, et al. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl* 2003;9:138–143.

Reprint requests

Address requests for reprints to: Patrick Northup, MD, Division of Gastroenterology and Hepatology, University of Virginia, JPA and Lee Street, MSB 2142, POB 800708, Charlottesville, Virginia 22908-0708. e-mail: northup@virginia.edu; fax: (434) 244-7529.

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by unrestricted educational grant for development of coagulation symposium from Vital Therapies, Inc and Hemosonics, Inc.