Management of Coagulation and Anticoagulation in Liver Transplantation Candidates

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Hemostasis is a complex balance of clot formation and dissolution that is largely modulated by protein synthesis and degradation in the liver. In the state of end-stage liver disease, there is a disruption of the hemostatic system due to hepatic protein synthetic dysfunction. Because historical clinical laboratory testing often only analyzes a portion of the hemostasis system, the clinician may be misled into believing that cirrhosis patients are imbalanced with a tendency toward bleeding. The modern understanding of hemostasis in cirrhosis involves a rebalance of hemostasis with a tenuous equilibrium between clotting and bleeding, but an equilibrium nonetheless. The clinician should be aware of this rebalance and not depend on limited and flawed laboratory testing in making judgments about the tendency for bleeding or clotting based on these values alone. Prophylactic protocol transfusions including large doses of fresh frozen plasma to "correct" the international normalized ratio are good examples of ineffective and potentially harmful interventions based on an outdated understanding of hemostasis in cirrhosis. Conversely, a thrombotic state is increasingly recognized in patients with cirrhosis, and conditions such as portal vein thrombosis are now becoming important therapeutic targets in many liver transplantation (LT) candidates and other patients with chronic liver disease. This article will introduce the reader to the modern understanding of hemostasis in cirrhosis, describe the common pitfalls and opportunities in treating hemostasis system abnormalities in the LT candidate particularly in regards to preprocedural prophylactic transfusions, and discuss therapeutic targets and interventions for thrombotic complications in the end-stage liver disease population.

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The care of the patient with chronic liver disease and liver cirrhosis has significantly evolved over the past 20 years. Better medical and surgical management of the complications of portal hypertension as well as new disease-specific therapies have led to an increase in survival of cirrhosis patients and, consequently, a need for better longterm management of decompensated liver disease. With the advent of liver transplantation (LT) as a definitive therapy for decompensated liver disease and modern donor organ allocation models that prioritize "sickest first," more patients are reaching transplantation with significant abnormalities in hemostasis caused by the protein synthetic dysfunction synonymous with end-stage liver disease. Similarly, data regarding the negative impact of portal vein thrombosis (PVT) on post-LT outcomes have led to more LT candidates being treated with chronic prophylactic or therapeutic anticoagulation while awaiting LT. Although there have been significant advances in the understanding of the hemostatic system in decompensated liver disease,[1] there is still a paucity of randomized trials in this area due to the complexity of studying this population and the lack of strong clinically predictive markers of bleeding risk and hemostasis. Despite the minimal clinical trial data in this area, hepatologists and LT teams are regularly confronted with difficult treatment decisions regarding coagulation and hemostasis, and many

Abbreviations: aPTT, activated partial thromboplastin time; DOAC, direct-acting oral anticoagulant; ETP, endogenous thrombin potential; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; PVT, portal vein thrombosis; ROTEM, rotational thromboelastometry; TAFI, thrombin-activatable fibrinolysis inhibitor; TEG, thromboelastography; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator; VKA, vitamin K antagonist; vWF, von Willebrand factor.

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management decisions are grounded in dogma based on outdated knowledge of the field. This article will cover the modern understanding of the rebalanced hemostatic system in decompensated liver disease and the pathophysiologic and clinical evidence behind management recommendations related to hemostasis in the LT candidate and patients with end-stage liver disease.

Pathophysiology: The Modern Understanding of Hemostasis in Decompensated Liver Disease

Normal hemostasis is the physiological process of stopping hemorrhage at a site of vascular injury while avoiding thrombosis at uninjured sites in the rest of the body. The hemostasis process can be divided into 3 main components: primary hemostasis, secondary hemostasis, and fibrinolysis. Primary hemostasis, which refers to the formation of a platelet plug at the site of injury, is dependent on platelet adhesion, activation, and aggregation. Platelet plug formation is critical in initial containment of blood loss and provides the active surface that localizes and accelerates the fibrin formation that ultimately produces a stable clot. Secondary hemostasis, or coagulation, involves the proteolytic coagulation cascade system that ultimately results in conversion of fibrinogen to fibrin, which then forms a mesh-like matrix in and around the platelet plug to strengthen and stabilize the clot. The last of the 3 components of hemostasis is the fibrinolysis pathway, which plays a significant role by containing the clot and preventing overpropagation. Fibrinolysis results in clot dissolution and is initiated endogenously as plasminogen is converted to plasmin by tissue plasminogen activator (t-PA). All 3 of these aspects of hemostasis are affected by liver disease.

Chronic liver disease, particularly in the advanced or decompensated stages, has historically been regarded as an example of an acquired bleeding diathesis primarily based on abnormalities in basic conventional laboratory tests of coagulation such as the prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). However, evidence over the past 20 years has developed to support the concept that the hemostatic system is "rebalanced" in patients with cirrhosis.[2]

Primary hemostasis is influenced by the thrombocytopenia of liver disease,[3,4] though quantitative deficits in platelet count are balanced by an increase in von Willebrand factor (vWF) and low levels of the vWF-cleaving protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).[4] Secondary hemostasis, or coagulation, is impacted by the synthetic dysfunction of cirrhosis resulting in decreased levels of procoagulant factors II, V, VII, IX, X, XI, and fibrinogen. Deficits in procoagulants are countered by proportionally decreased levels of anticoagulant proteins including protein C and protein S, antithrombin, and heparin cofactor II, as well as increased levels of factor VIII, which end up rendering a preserved hemostatic equilibrium in stable cirrhosis. There are now ample studies in cirrhosis patients to demonstrate that despite abnormalities in conventional coagulation tests, patients with liver disease are able to generate sufficient thrombin for clot formation, indicating a preserved clotting state.[5,6] In fact, other recent studies suggest that thrombin generation is exaggerated in patients with acute decompensated cirrhosis[7] and may result in a tendency to shift toward a hypercoagulable state in many patients. Decreased levels of protein C (1 of the most potent natural anticoagulants) and elevated factor VIII levels that are typical of cirrhosis may further promote this shift toward a prothrombotic imbalance.[8,9]

Although their use as a prognostic index for the severity of liver disease has been well demonstrated, conventional laboratory tests of coagulation, specifically PT and its derivative the INR, do not provide clinically relevant information regarding bleeding or thrombotic risk in patients with such complex alterations of the

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hemostatic system as seen in cirrhosis. PT measures the extrinsic and final common pathway of coagulation (factor II/prothrombin, V, VII, X, fibrinogen, and tissue factor) and is heavily dependent on vitamin K, whereas INR is merely a mathematical conversion of the PT devised to normalize results to account for variations in reagents used among laboratories and was conceived to be used in monitoring patients on therapeutic warfarin. Neither PT nor INR accurately reflects the in vivo coagulation status of patients with liver disease because these tests only measure the levels of procoagulant proteins and fail to account for the concurrent alterations in anticoagulant proteins or platelets that are known to occur in these patients.[6] As a result, PT and INR are no longer accepted as means of determining thrombotic or bleeding risk in patients with cirrhosis. Clinicians should avoid making medical decisions on the basis of these values alone without properly assessing the other components of the system. Recent commercially available tools such as thromboelastography (TEG), rotational thromboelastometry (ROTEM), and thrombin generation assays provide a more accurate assessment of the entire hemostatic system and are being brought forward for more accessible use in direct patient care.

The balance between procoagulant systems and anticoagulant systems is crucial for proper hemostasis and the avoidance of pathological bleeding or thrombosis. In patients with decompensated liver disease, abnormalities exist in primary hemostasis, coagulation, and fibrinolysis due to quantitative and qualitative changes in platelets, procoagulant factors, and antithrombotic and antifibrinolytic proteins. Although some of these changes result in reduced prohemostatic capacity, they are offset by the loss of anticoagulant processes. Figure 1 depicts the rebalance of hemostasis in cirrhosis. The hemostatic balance in cirrhosis is tenuous and can be easily tipped toward bleeding or thrombosis, depending on the prevailing risk factors and/or systemic disturbances as described below. Table 1 summarizes some of the major pathophysiologic studies supporting the rebalance in prohemostatic and antihemostatic forces in end-stage liver disease.

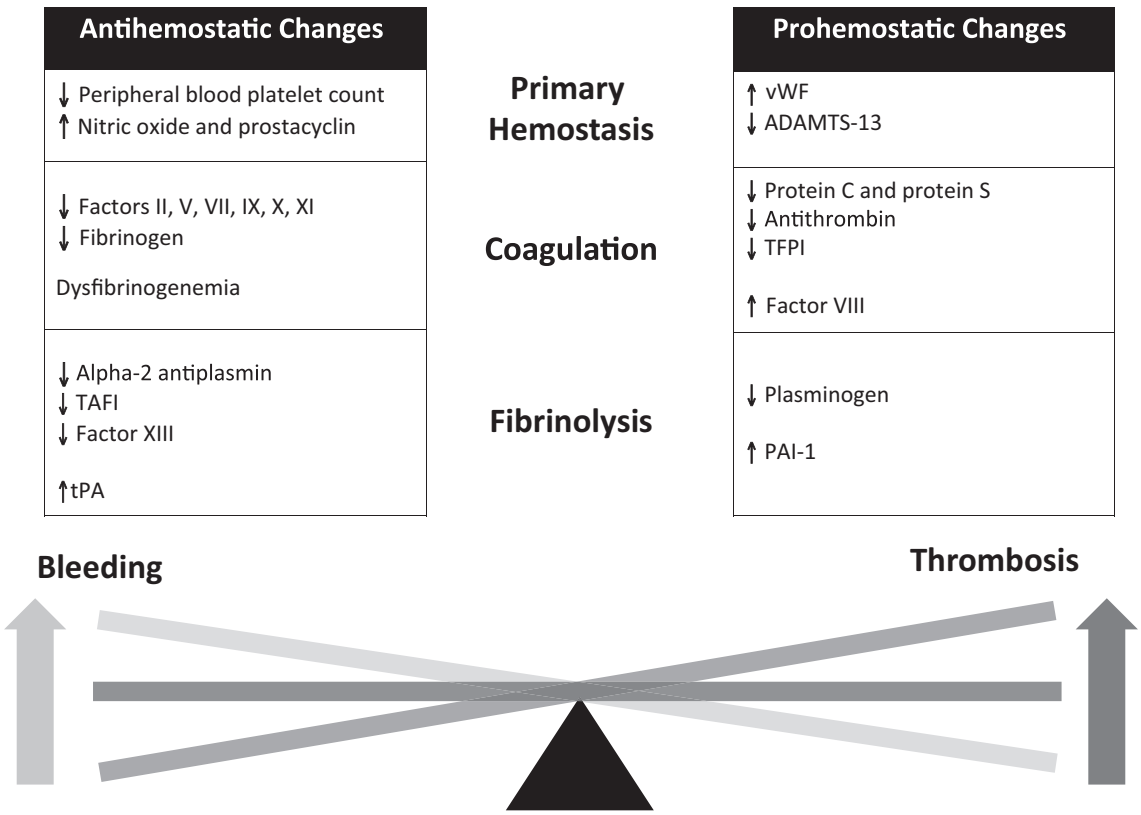

FIG. 1. The rebalance of hemostasis in cirrhosis.

TABLE 1. Pathophysiologic Studies Supporting a Rebalanced Hemostasis System in Patients With Cirrhosis and End-Stage Liver Disease

Author/Year	Aspect of Hemostasis Studied	Population	Assays Used	Result	Take-Home Point
Tripodi et al.[5] (2005)	Thrombin generation	44 patients with cirrhosis CPT A 32% CPT B 36% CPT C 32% 44 healthy controls	Thrombin generation measured as the ETP Assays performed with and without the addition of soluble thrombomodulin, which allows full activation of protein C	In the presence of thrombomodulin, patients with liver cirrhosis generated equally as much thrombin as control subjects (median ETP 209 FU/minutes versus 188 FU/minutes in controls, $P = 0.50$)	In cirrhosis, the reduction of factor II (procoagulant drive) is balanced by the reduction of protein C (anticoagulant drive), resulting in an unaltered coagulation system
Tripodi et al.[3] (2006)	Platelets; Thrombin generation	87 patients with cirrhosis CPT A 45% CPT B 38% CPT C 17% 62 healthy controls	Thrombin generation measured as the ETP. Assays performed with the addition of soluble thrombomodulin	In patients with cirrhosis, a minimum platelet count of 56 k/mcL was necessary to generate thrombin levels comparable to that of healthy controls	Significant thrombocytopenia (platelet count <56 k/mcL) may reduce thrombin generation capability
Lisman et al.[4] (2006)	vWF; Platelet adhesion	54 patients with cirrhosis CPT A 35% CPT B 32% CPT C 33% 5 patients with acute liver failure 40 healthy controls	vWF antigen levels vWF ristocetin cofactor activity vWF collagen-binding activity ADAMTS13 antigen levels and activity Multimeric vWF structure vWF propeptide levels vWF-dependent platelet adhesion assay performed under flow conditions	vWF levels are markedly elevated in patients with liver disease and directly correlate with disease severity, though the functional capacity of vWF is reduced Despite decreased functional capacity of vWF, the highly elevated vWF levels in plasma from patients with liver disease result in significantly greater platelet adhesion compared with plasma from normal healthy controls	Plasma from patients with cirrhosis supports vWF-dependent platelet adhesion better than plasma from normal healthy controls
Tripodi et al.[9] (2009)	Antithrombin, protein C, factor V, factor II, factor VIII, and thrombin generation	134 patients with cirrhosis CPT A 40% CPT B 43% CPT C 17% 6 patients with known congenital protein C deficiency without cirrhosis 131 healthy controls	Thrombin generation was measured as ETP, and assays were performed in the presence and absence of thrombomodulin; results expressed as ETP ratio (with/without thrombomodulin) Factor II measured as procoagulant activity upon activation with Taipan snake venom Factor V and VIII, antithrombin, and protein C assays	When compared with healthy subjects, patients with cirrhosis had significantly prolonged PT, reduced levels of antithrombin, protein C, factor V and factor II, and increased levels of factor VIII ($P < 0.01$) The median ETP ratio value for the patient population (0.80) was significantly higher than that of healthy subjects (0.66; $P < 0.01$) and similar to that of patients with congenital protein C deficiency ($P = 0.47$) Ratios of factor V:protein C, factor VIII:protein C, and factor VIII:antithrombin were significantly higher in patients with cirrhosis compared with healthy controls (all $P < 0.01$)	In cirrhosis, the ratio of the most powerful procoagulants and anticoagulants operating in plasma are considerably in favor of the former, thus shifting toward a state of hypercoagulability

TABLE 1. ***Continued.***

Lisman et al.[6] (2010)	Thrombin generation	10 patients undergoing LT Mean MELD score 18 (range 11-27) 40 healthy controls	Thrombin generation assays performed with the addition of soluble thrombomodulin ETP Peak thrombin concentration Time to peak Thrombin generation velocity	Thrombin generation in patients undergoing LT was equal to or even higher than that of healthy subjects when tested in the presence of thrombomodulin ($P < 0.05$). Peak thrombin generation and the velocity of thrombin generation were significantly higher in the postoperative period compared with controls ($P < 0.01$ for both).	The coagulation capacity of patients with severe liver disease undergoing LT is normal or even elevated compared with healthy controls. These patients may even be at increased risk for thromboembolic complications postoperatively due to a hypercoagulable state.
Tripodi et al.[8] (2013)	Protein C	50 patients with cirrhosis CPT A 32% CPT B 50% CPT C 18% 5 patients with known congenital protein C deficiency without cirrhosis >50 healthy controls	Thrombin generation was measured by an assay performed in the presence/absence of thrombomodulin and a second assay performed in the presence/absence of Protac (a potent protein C activator) Results for 2 thrombin generation assays were expressed as ratios of ETP with-to-without thrombomodulin or as Protac-induced coagulation inhibition (PICI%)	In patients with cirrhosis, the median protein C functional activity was 40% before the addition of protein C and increased to 260% after ($P < 0.01$) Patients with cirrhosis had a median ETP ratio (0.83) greater than the upper limit of reference range (0.81) before the addition of protein C. The ETP ratio decreased in a dose-dependent fashion with the addition of increasing quantities of protein C ($P < 0.01$). Similar results were seen with the Protac assay in which cirrhosis patients had a lower baseline PICI% that improved with the addition of protein C	Low protein C contributes to the procoagulant imbalance in cirrhosis as evidenced by resistance to the in vitro anticoagulant action of thrombomodulin or Protac

In summary, the modern understanding of the physiology of hemostasis involves several closely linked systems including primary hemostasis, which is largely platelet-based, secondary hemostasis, traditionally thought of as coagulation, and fibrinolysis, the system involved in restraining pathologic clot propagation. Decompensated liver disease leads to disruption and rebalance of all phases of hemostasis including both the prohemostatic and antihemostatic pathways. Because of this rebalance, an individual liver disease patient is not necessarily predisposed to bleeding or clotting at baseline. Traditional laboratory testing parameters such as the INR and platelet count reflect only small parts of individual components of the hemostasis system and are not directly reflective of the clotting or bleeding status of a specific patient.

Procedural Bleeding Risk Stratification and Prophylaxis Strategies

PROBLEMS WITH THE INR AS A BLEEDING RISK MEASURE

The INR and PT are inexorably linked to the prognosis of cirrhosis as a reflection of protein synthesis dysfunction. The Child-Turcotte-Pugh and Model for End-Stage Liver Disease (MELD) scores are 2 well-known examples demonstrating a direct correlation between PT/INR and mortality as well as common complications of portal hypertension including bleeding from esophageal varices, ascites formation, and hepatic encephalopathy. The clinical management of these portal hypertension complications is beyond the scope of this article and covered in depth in many practice guidelines and review articles. Despite the PT/INR correlation with prognosis and complications of portal hypertension, many practitioners in the past have misinterpreted an elevated INR as an indicator of bleeding risk in patients with cirrhosis and incorrectly concluded that correcting the INR to a normal range reduces bleeding risk back to baseline, especially in the setting of invasive procedures. This false perception has been disproven in multiple studies across a wide array of procedures including therapeutic paracentesis,[10] transjugular liver biopsy,[11] laparoscopic liver biopsy,[12] arterial needle punctures during cardiac catheterization,[13] and even in the setting of

LT.[14] Therefore, the status of this rebalanced system in any individual patient is not easily measured by routine laboratory assessments such as the PT/INR or complete blood count. Plus, interventions promoting clot formation (eg, plasma infusions or factor replacement therapy) do not address imbalances in the other components of the hemostasis system and may in fact be harmful to the patient. Although there are minimal data, it would seem clinically reasonable that INR values in the extreme high range (>3) would present more bleeding risk than baseline, but this is not quantified in the literature. Data in acute liver failure support a reasonably balanced hemostasis system and minimal bleeding complications[15] despite extremely high INR levels. It is important for the practitioner to understand the concept of a rebalanced hemostasis system in cirrhosis and avoid needless and potentially harmful transfusions that are not supported by the literature, especially in the setting of procedural prophylaxis.

In summary, INR is not predictive of bleeding risk in cirrhosis patients, except perhaps at the extreme range of elevations, and should not be used as a measure of procedural bleeding risk.

MODIFIABLE RISK FACTORS FOR PRECEDURAL BLEEDING: GENERAL CONSIDERATIONS, RENAL FAILURE, AND ACTIVE INFECTION

In addition to the innate protein synthetic dysfunction of decompensated cirrhosis, there are several factors that can contribute to hemostasis disruption in the LT candidate. First of all, a history of pathologic bleeding or clotting should be sought during the initial evaluation of the cirrhosis patient. Full exploration of the patient's personal and family history of potential inherited bleeding or clotting disorders may help elucidate a potential risk factor and guide more detailed consultation or specific prophylactic intervention. Similarly, traditional risk factors for thrombophilia should be assessed and considered in the overall treatment and risk stratification of the transplant candidate. For example, hepatocellular carcinoma (HCC) is very common in this population and has been shown to predispose to a hypercoagulable state.[16] Malignant invasion of the portal vein must be ruled out, however, in the transplant candidate presenting with PVT in the setting of HCC. Finally, the clinical stage of decompensation has major implications in the hemostasis situation of the patient. For example, the rapidly deteriorating patient with acute-on-chronic liver failure may have a more systemic bleeding tendency related to systemic inflammation and multiorgan dysfunction.[17] In contrast, acute liver failure has shown a possible propensity for thrombosis despite the hallmark elevation in INR.[15]

MELD incorporates creatinine into the organ allocation scheme, and alterations in liver allocation over recent years have placed an emphasis on patients with renal failure resulting in more patients with acute and chronic renal failure undergoing LT. Although the pathophysiologic explanation is not completely clear, data support an increased bleeding risk in patients with chronic renal disease, especially those on hemodialysis. One study showed a bleeding rate of 40% in chronic kidney disease patients and 45% in those on hemodialysis and proposed that platelets in uremic patients were hyporesponsive to stimulation of glycoprotein IIb/IIIa antigen membrane expression compared with controls thereby leading to less platelet aggregation.[18] Although this deleterious platelet effect is improved with hemodialysis, there is no clear clinical data showing improved bleeding rates in patients after dialysis sessions. The data for platelet dysfunction are less clear with acute uremia and acute kidney injury. In the setting of acute kidney injury due to acute liver failure, no increase in bleeding was seen in a series of 20 consecutive patients despite significant thrombocytopenia.[19] The authors of this study noted a compensatory increase in vWF, which blunted the clinical effect of the thrombocytopenia in these patients. Although no data clearly show that renal replacement therapy improves bleeding risk in the uremic patient, it would seem reasonable to delay elective procedures that carry a high risk of bleeding in the cirrhosis patient with renal failure until renal function is restored or effective renal replacement therapy is instituted, if clinically possible.

In addition to renal dysfunction, another general condition associated with increased bleeding risk is systemic infection. A landmark study in 2002 compared 30 cirrhosis patients with active severe infection with 30 cirrhosis patients not actively infected.[20] Through the use of heparinase-modified TEG, the investigators detected an innate heparin effect on hemostasis in the cohort with infection, which was not seen in the uninfected cohort. This effect completely reversed after the infection was fully treated. These endogenous heparinoids are hypothesized to be

released during the general endothelial activation of systemic infection. Clinically, active infection has been prospectively shown to be independently associated with failure to control gastrointestinal bleeding in cirrhosis patients.[21] Similarly, antibiotic prophylaxis for infection has been incorporated into esophageal variceal bleeding management practice guidelines not only to prevent systemic infection after bleeding but also because infection prevention led to decreased rebleeding rates and less blood utilization.[22] For the clinician, prevention or control of systemic infection in the patient with cirrhosis prior to elective procedures could be another factor that is under the control of the medical team to potentially help decrease bleeding risk.

In summary, a thorough history and physical examination related to bleeding or clotting abnormalities should be performed in every transplant candidate. Acute and chronic renal failure and systemic infection are modifiable risk factors for procedural bleeding and should be aggressively treated prior to all elective procedures with bleeding risk.

Understanding the above general medical interventions that can improve bleeding risk in the LT candidate, there are several specific circumstances in which intervention in the segment of the hemostasis balance has been evaluated in clinical trials or cross-sectional studies. Many of these studies focus on the most common exposure to bleeding risk in the LT candidate: invasive and percutaneous procedures.

PERIPHERAL PLATELET COUNT THRESHOLDS AND INTERVENTIONS

Quantitative deficits in circulating platelet counts are a hallmark of portal hypertension and are due to a combination of splenic sequestration and innate decrease in thrombopoietin secretion in the diseased liver.[23] Little research has been undertaken to investigate adequate thresholds of platelets to allow clot formation in the patient with cirrhosis. Tripodi et al.[3] investigated thrombin generation in plasma from cirrhosis patients and found that a platelet count of 56 k/mcL allowed thrombin generation at the 10th percentile of the healthy control population. Moreover, there was little added increase in thrombin generation with a platelet count of >100 k/mcL. However, despite this encouraging data in vitro, when the same group investigated platelet transfusion practices in their hospital they found little improvement in platelet counts after prophylactic platelet transfusions prior to elective variceal band ligation and little resulting effect on global coagulation or thrombin generation.[24] A large prospective study of complications of liver biopsy in cirrhosis patients was published by Seeff et al.[25] and demonstrated potentially serious bleeding in 0.5% of the cohort. Analysis showed that the population with platelets <60 k/mcL had the highest relative risk of bleeding (4 or 15 bleeding events), but numerically, more bleeding events occurred in patients with platelet counts of >100 k/mcL (8 of 15). The authors concluded that there was an increased risk of bleeding in percutaneous liver biopsy with platelet counts of <60 k/mcL.

Very few studies have examined platelet thresholds for low bleeding risk procedures because of the very low event rates after these procedures. For instance, the American Association for the Study of Liver Diseases practice guidelines for management of adult patients with ascites due to cirrhosis[26] do not recommend specific thresholds for coagulation parameters in performing therapeutic paracentesis. To summarize, physiologic in vitro and observational clinical data suggest that a platelet threshold of approximately 56 k/mcL would offer enough platelet function to generate adequate clots in cirrhosis patients prior to high bleeding risk procedures. Patients undergoing low bleeding risk procedures generally do not benefit from prophylactic platelet transfusion.

In summary, a platelet threshold of approximately 56 k/mcL should be adequate to allow the cirrhosis patient to form a clot based on in vitro studies. Interventions to increase platelet counts to higher levels prior to invasive procedures have not been tested in randomized controlled trials and cannot be recommended based on available data.

THE INR AND FRESH FROZEN PLASMA TRANSFUSION

As stated previously, the INR is generally not useful in predicting bleeding complications related to procedures in patients with cirrhosis and target thresholds for preprocedural INR are not based on sound physiologic, experimental, or clinical data. Furthermore, when clinicians treat cirrhosis patients with elevated INR values, they tend to try and replete coagulation factor deficiencies with fresh frozen plasma (FFP). Transfusion medicine textbooks generally recommend between 15 and 30 mL/kg of FFP in order to correct an INR to 1.5 resulting in the need of 1-2 L of FFP (5-10 units of 200 mL FFP).[27] This level of transfusion is impractical in

the prophylactic setting and rarely, if ever, logistically accomplished by the clinician. An observational study of transfusion practices in cirrhosis patients prior to cardiac catheterization from a single center[13] showed the mean number of FFP units given prophylactically was between 2 and 4 and not surprisingly, only 1 of the 157 patients in the study had an INR < 1.9 after completion of the transfusions. In this study, despite inadequate transfusions and lack of INR correction, there were no major vascular complications or procedure-related bleeding events. This lack of efficacy and inadequate transfusion might seem harmless, but there is a growing understanding of transfusion complications such as transfusion-related lung injury[28] and frank volume overload that can place patients at great risk. Further compounding the issue is the fact that some practice guidelines and treatment paradigms tend to group patients with an elevated INR due to therapeutic anticoagulation or congenital factor deficiencies with chronic liver disease patients despite the overwhelming preponderance of physiologic and clinical data to contradict that similarity. As a general recommendation in relation to INR thresholds for procedures in patients with chronic liver disease, there is no data-supported INR level that decreases risk of bleeding. Prophylactic FFP transfusions are nearly always inadequate, ineffective, and are associated with life-threatening complications. Therefore, their use in this setting is not recommended until definitive peer-reviewed data regarding their efficacy are established.

In summary, the enormous majority of published data suggest that using FFP transfusion to decrease INR prior to invasive procedures in cirrhosis patients does not alter bleeding risk in any clinically measurable way. Because of the potential massive volume of FFP needed, routine prophylactic transfusion of FFP prior to procedures carries significant risk. On the basis of the available clinical trial and epidemiologic data, there is no indication to transfuse cirrhosis patients with FFP prior to elective procedures as a means to decrease bleeding risk.

FIBRINOGEN LEVELS AND FIBRIN DEFICITS

Clinicians caring for patients with liver disease often are confronted with abnormal bleeding due to hyperfibrinolysis, although the formal diagnosis is not frequently identified or established. In patients with chronic liver disease, the syndrome of hyperfibrinolytic bleeding consists of steady venous oozing of blood from mucosal or epidermal puncture sites such as central venous catheters, hemodialysis lines, sockets after dental extractions, or colon polypectomy sites. The bleeding often spreads subcutaneously, for instance after paracentesis, and can be steady and severe, though it is rarely brisk or immediately life-threatening. The syndrome most often presents in the patient with advanced liver disease, frequently in the setting of severe acute alcoholic hepatitis or alcoholic cirrhosis. Because of the pathophysiology of inappropriate clot breakdown is likely due to local persistence of innate anticoagulants such as t-PA,[29] the clinical bleeding is often not evident until several hours after the procedure. Diagnostic testing for this disorder is typically not readily available to the clinician, and traditional systemic viscoelastic testing (ie, TEG or ROTEM) is usually not sensitive enough to detect the local changes attributed to this disorder. Specialized laboratory testing indicative of this disorder include the euglobulin clot lysis time, the plasminogen assay, and the alpha-2-antiplasmin assay but none of these tests are readily available in most clinical labs. The disorder is most often diagnosed clinically and if the diagnosis is suspected and other causes of inappropriate clot breakdown are ruled out, treatment with epsilon-aminocaproic acid has been shown in a small series to be efficacious.[30]

Low fibrinogen levels have long been associated with poor outcomes in patients with hemorrhage and trauma. Similarly, low fibrinogen levels are common in decompensated cirrhosis patients, but a direct relationship between low fibrinogen levels and bleeding complications has been difficult to assess. A large prospective study of 1493 critically ill patients (211 with cirrhosis) was conducted to assess for risk factors for bleeding in patients during a critical care admission.[31] The investigators found that a platelet count of <30 k/mcL, fibrinogen level of <60 mg/dL, and aPTT of >100 seconds were all independently associated with increased major bleeding risk in the patients with cirrhosis. There was no interventional arm in the trial, but in the patients who received coagulation product transfusion, the investigators noted no significant difference in the amount of blood product transfusions used comparing patients with cirrhosis to those without. On the basis of the results of this study, no recommendation can be made on fibrinogen repletion in the critically ill cirrhosis patient, although it would seem physiologically sound that fibrinogen repletion with cryoprecipitate to provide enough fibrin to establish a proper

clot would be beneficial for the bleeding or high-risk patient. The threshold for adequate fibrinogen levels in this situation has not been studied.

In summary, the usually clinically diagnosed syndrome of hyperfibrinolysis should be suspected in delayed puncture site and mucosal bleeding and frequently responds to epsilon aminocaproic acid. Fibrinogen levels of <60-100 mg/dL are associated with major bleeding events in critically ill cirrhosis patients. It is unknown whether fibrinogen replacement therapy changes that risk.

VISCOELASTIC TESTING AND RISK STRATIFICATION

Viscoelastic tests, such as TEG and ROTEM, are becoming more commonly used during LT to guide periprocedural blood product management.[32] These tests use whole blood to measure shear strength of the clot continuously, mimicking in vivo conditions. Details about TEG and ROTEM are beyond the scope of this article but are described in great detail elsewhere.[33] All components of the hemostatic system are analyzed including platelet function, coagulation proteins, and fibrinolysis, and each is reported separately, allowing for more specific interventions. TEG/ROTEM can be used to guide transfusion of platelets, FFP, cryoprecipitate, and fibrinogen concentrate, as well as administration of antifibrinolytics. TEG/ROTEM–based transfusion and coagulation management algorithms have been shown to reduce transfusion requirements and cost during major surgery and LT.[34] A small, randomized prospective study in LT patients showed a significant reduction in transfusions in the TEG monitored group compared with the standard coagulation test group, most notably in the use of FFP.[35] Ongoing clinical trials using ROTEM and fibrinogen in LT are expected to provide guidance on optimization of blood product utilization in the immediate preoperative and intraoperative period (clinicaltrials.gov identifiers NCT02987712 and NCT02362178). Although TEG and ROTEM have been used in the operating room environment extensively, they have shown more uncertain predictive ability in less invasive procedures, and data are sparse for their application in day-to-day bleeding risk stratification, especially in outpatients. A single randomized controlled trial has been performed in decompensated cirrhosis patients with significant abnormalities in traditional coagulation parameters undergoing mainly outpatient endoscopy.[36] The authors of this study concluded that TEG helped decrease blood product transfusion prior to elective procedures in patients with cirrhosis. Although the standard of care in this study was FFP transfusion, which as mentioned previously is not an intervention that is likely to prevent procedural bleeding (only 1 case of bleeding was documented in the study), this study was beneficial in its demonstration that protocol transfusions should be based on objective parameters outside of the INR and platelet count.

In summary, viscoelastic testing such as TEG and ROTEM have been used to guide transfusion strategy in cirrhosis patients undergoing major surgical procedures with some success in avoiding protocol transfusions. These technologies are less studied in minor procedures and outpatient scenarios.

PVT in the Pretransplant Setting

EPIDEMIOLOGY AND NATURAL HISTORY OF PVT

PVT is a well-recognized phenomenon in patients with liver cirrhosis and in the setting of hepatobiliary surgery and LT. Traditionally, malignant invasion of the portal vein due to vascular spread of HCC is the most commonly encountered form of PVT, and the management of this disorder is more targeted to the management of the primary malignancy. In the setting of cirrhosis, the occurrence of benign or bland PVT presents the clinicians with more of a management and prognostic challenge. In the LT candidate, extensive PVT thromboses requiring nonanatomic venous anastomoses or bypass grafts increase the technical challenge and length of the transplant operation and are associated with a near 2-fold increase in hazard ratio of 30-day mortality independent of other donor and procedural factors.[37] Because of the various types and grading systems for PVT, the prevalence of PVT in cirrhosis patients ranges from 6.6% in an angiographic study[38] to as high as 14% at autopsy in cirrhosis patients with malignancy.[39] Specifically in LT candidates at the time of transplantation, the prevalence of nontumor PVT ranges from 4.5%[37] to 6.3%.[40]

In the nontransplant setting, the significance of PVT is less clear. In a prospective study of 1243 patients with cirrhosis undergoing screening for HCC,[41] PVT was not found to be independently associated with progression of liver disease, and the authors

speculated that PVT was a result of worsening portal hypertension and liver fibrosis and not a cause of decompensation per se. In contrast, epidemiologic data specifically in the LT population[40] have directly associated the presence of PVT with an increased wait-list mortality, especially in patients with nonalcoholic steatohepatitis. Similarly, in a much criticized but randomized controlled trial, patients at high risk for PVT were randomized to PVT prophylaxis with low-molecular-weight heparin (LMWH) or standard of care for 48 weeks.[42] In this study, the patients exposed to PVT prophylaxis not only had effective prevention of PVT formation during administration of the LMWH but had a durable and persistent advantage in progression of portal hypertension and overall survival. The combination of the high suspicion of PVT causing adverse transplant outcomes and the possibility of PVT prevention leading to improvement in cirrhosis outcomes has led to a great interest in treatment and prevention of PVT in the decompensated cirrhosis population, especially those eligible for LT. Recent consensus guidelines for the management of portal hypertension include recommendations for treatment and monitoring of PVT in decompensated cirrhosis based on expert opinion.[43]

In summary, PVT is variable in prevalence but is associated with worsened posttransplant outcomes. It is unclear whether pretransplant PVT leads to accelerated decompensation of liver disease and portal hypertension or whether PVT is simply a marker of worsening portal hypertension and liver fibrosis.

TREATEMENT STRATEGIES FOR PVT IN THE TRANSPLANT CANDIDATE

In transplant candidates, aside from mechanical thrombectomy at the time of transplantation, there are 2 categories of therapy in regards to PVT: (1) systemic therapeutic medical anticoagulation and (2) intravascular stenting of the obstructed portal vein via either a transhepatic or sometimes transplenic approach often in combination with mechanical or lytic thrombectomy.

MEDICAL ANTICOAGULATION THERAPY FOR PVT IN THE CIRRHOSIS PATIENT

Clinicians have used therapeutic anticoagulation for many decades in the general medical patient since the discovery of the vitamin K antagonists (VKAs) for various indications including deep vein thromboses and prophylaxis after surgical procedures. As described above, traditional fears of excess bleeding with therapeutic anticoagulation in patients with advanced liver disease due to misunderstood basic laboratory testing have hindered the use of these medications in this population. However, the modern understanding of rebalanced hemostasis in patients with cirrhosis has led providers to be more pragmatic in the use of medical anticoagulation in this population. A 2015 systematic review[44] identified more than 16 published series with safety and efficacy endpoints in cirrhosis patients undergoing therapeutic medical anticoagulation for PVT. Although there have not been randomized, blinded, controlled trials published in this area, some conclusions from the published literature can be extrapolated.

Traditionally, warfarin and the other VKAs have been used in thrombotic disease in patients without cirrhosis due to broad clinician experience, relatively low cost, and monitoring availability using the validated INR system. As mentioned above, however, the INR system is disrupted in liver disease patients and is elevated at baseline in most cirrhosis patients. In addition, the VKAs also decrease protein C activity (which is also vitamin K–dependent) and evidence suggests a significant protein C deficiency leading to thrombophilia in advanced cirrhosis patients.[8] This combination of difficulty in monitoring VKA activity and a physiologically rational potential for paradoxical thrombophilia in cirrhosis patients makes the VKAs less than ideal for medical therapeutic anticoagulation in this population. The literature supports the existence of a narrow therapeutic window with VKAs in cirrhosis patients who have any significant elevation in baseline INR, and these patients are likely more prone to complications from this type of therapy.[45]

The bulk of the literature on medical therapeutic anticoagulation in this population involves the LMWH molecules and the modern direct-acting oral anticoagulants (DOACs). There are more than 10 reported case series or controlled studies investigating either LMWHs or DOACs in the treatment or prevention of PVT in cirrhosis patients, and safety and efficacy data are accumulating.[44] The attraction of LMWH is the shorter half-life compared with the VKAs and the significant accumulated safety and efficacy data.[42,46] The injectable-only formulation of LMWH is a significant negative related to patient adherence and acceptance of longterm therapy. Additionally, renal dysfunction limits the use of

the LMWH compounds, and fully functional reversal agents are limited. It should be noted that dosing of the LMWH compounds based on anti-Xa activity, a common practice in many medical centers in the United States, can inadvertently lead to higher-than-expected anticoagulant levels in the patient because of the innate decrease in antithrombin associated with the progression of hepatic protein synthetic dysfunction.[47] This effect is especially pronounced in the higher Child-Pugh stages of disease and can lead to bleeding complications.[48] It is not recommended to use the anti-Xa activity assay as a LMWH dosing guide in cirrhosis patients with advanced disease, especially in the setting of severely decreased antithrombin levels prior to anticoagulation. Consultation with hematology experts is recommended in this situation.

The DOACs have the advantage of oral dosing and once or twice daily administration. See Table 2 below for a summary of currently available DOACs in the United States. Because of the relatively recent uptake of these agents for use in the general medical population, efficacy data are sparse with these agents in chronic liver disease although anecdotal evidence suggests reasonable efficacy in the therapy of PVT. Safety data are more forthcoming, and these agents appear to be generally as safe as LMWH in this population with severe bleeding rates similar compared with the general population.[49,50] Randomized controlled PVT prophylaxis studies using DOACs in cirrhosis patients are ongoing. A direct and efficacious reversal agent for anticoagulants is highly desirable in the setting of transplantation when the time frame between the last dose of anticoagulant and major surgery is unpredictable by the nature of deceased donation. The only DOAC reversal agent approved by the US Food and Drug Administration is idarucizumab specifically for reversal of dabigatran,[51] and its successful use in the setting of LT has been reported.[52] A reversal agent for the other DOACs (and potentially LMWH) is currently in development, andexanet alfa, and it was given U.S. Food and Drug Administration approval in May 2018. The agent has limited availability at the time of this publication but plans for broad distribution are underway.

In summary, medical anticoagulation for the treatment of PVT in the transplant candidate has several theoretical advantages over mechanical therapies. Bleeding risk in cirrhosis patients placed on medical anticoagulation appears to be similar to the general population of medical patients on similar therapy with the possible exception of increased bleeding risk in the VKAs. LMWHs are the most tested anticoagulants in the cirrhosis population, but the DOACs are being used more commonly with promising initial results. Current and future reversal agents for the DOACs will give transplant teams more confidence in these agents in the immediate perioperative time period.

INTRAVASCULAR INTERVENTIONS AS A PVT THERAPY PRIOR TO TRANSPLANTATION

The intravascular approach has been successful in recanalization and maintenance of patency of the portal vein until transplant in uncontrolled small series,[53] although the procedure is technically demanding and generally only available at centers with significant expertise. Despite these reports of success, intravascular stenting is invasive, permanently alters anatomy, and carries risk of deleterious adverse effects such as hepatic encephalopathy, especially after transjugular intrahepatic portosystemic shunting, as well as procedural complications. It is also unclear whether therapeutic medical anticoagulation is needed after these procedures, especially if there

TABLE 2. The Current DOACs and Their US Food and Drug Administration Labeling

Agent	Dosing	Liver Disease	Renal Disease Dose Adjustment	Reversal Agent
Apixaban (Eliquis)	Twice daily	Child A and B	Yes	In approval process*
Betrixaban (Bevyxxa)	Once daily	Not recommended	Yes	In approval process*
Dabigatran (Pradaxa)	Twice daily	Child A and B	Yes	Yes, idarucizumab
Edoxaban (Savaysa)	Once daily	Child A only	Yes	In approval process*
Rivaroxaban (Xarelto)	Once daily	Child A only	Yes, contraindicated with creatinine clearance < 30 mL/min	In approval process*

*Andexanet alfa.

is predicted to be a long wait until transplantation. No randomized trials with controls have been performed with this technique, thus each center should exercise local expertise and judgment when approaching PVT with stenting and other intravascular approaches.

In summary, intravascular approaches to recanalization of the portal vein in the transplant candidate can sometimes be used in specialized centers even in the setting of advanced PVT.

Summary and Future Directions

Our understanding of the human hemostasis and coagulation system is incomplete, and the system is complex with many components still poorly understood. The disruption in this system caused by liver disease is much more than simply an elevated INR and lower circulating platelet counts. The tenuous rebalance of hemostasis in cirrhosis is only now beginning to be understood, and the knowledge that some cirrhosis patients have a tendency for abnormal clotting reinforces the sometimes counterintuitive nature of hemostasis. Dogma and protocol based on outdated and incomplete knowledge have clouded clinician judgment, and those practices still influence daily clinical decisions. Admittedly, the evidence is weak for many of the proposed practices in this article, but the evidence is weak for historically established current practices as well. Traditional laboratory testing gives very incomplete and one-sided information that can lead the well-meaning clinician to put the patient at risk for minimal potential benefit. Viscoelastic testing and newer laboratory assays that are making it slowly to the clinical laboratory may help give a more complete picture of hemostasis in the cirrhosis patient of the future. In treating the liver disease patient, addressing exacerbating conditions like advanced acute or chronic renal disease or ongoing infection should be a priority. With platelet counts greater than approximately 50 k/mcL, prophylactic FFP administration for all but the highest risk procedures is unlikely to benefit the patient and may cause harm through worsening of portal hypertension. In regards to thrombosis, PVT is strongly associated with worse LT outcomes and may prompt worsening of liver fibrosis and portal hypertension and as a result, more cirrhosis patients are being treated with anticoagulant medications for prophylaxis and therapy. With the possible exception of the VKAs, anticoagulants can be used safely in cirrhosis and with current and upcoming reversal agents are a viable option in patients awaiting LT. Future studies should be performed in the area of hemostasis in cirrhosis, and optimal treatment algorithms should be developed for the benefit of all patients awaiting LT.

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