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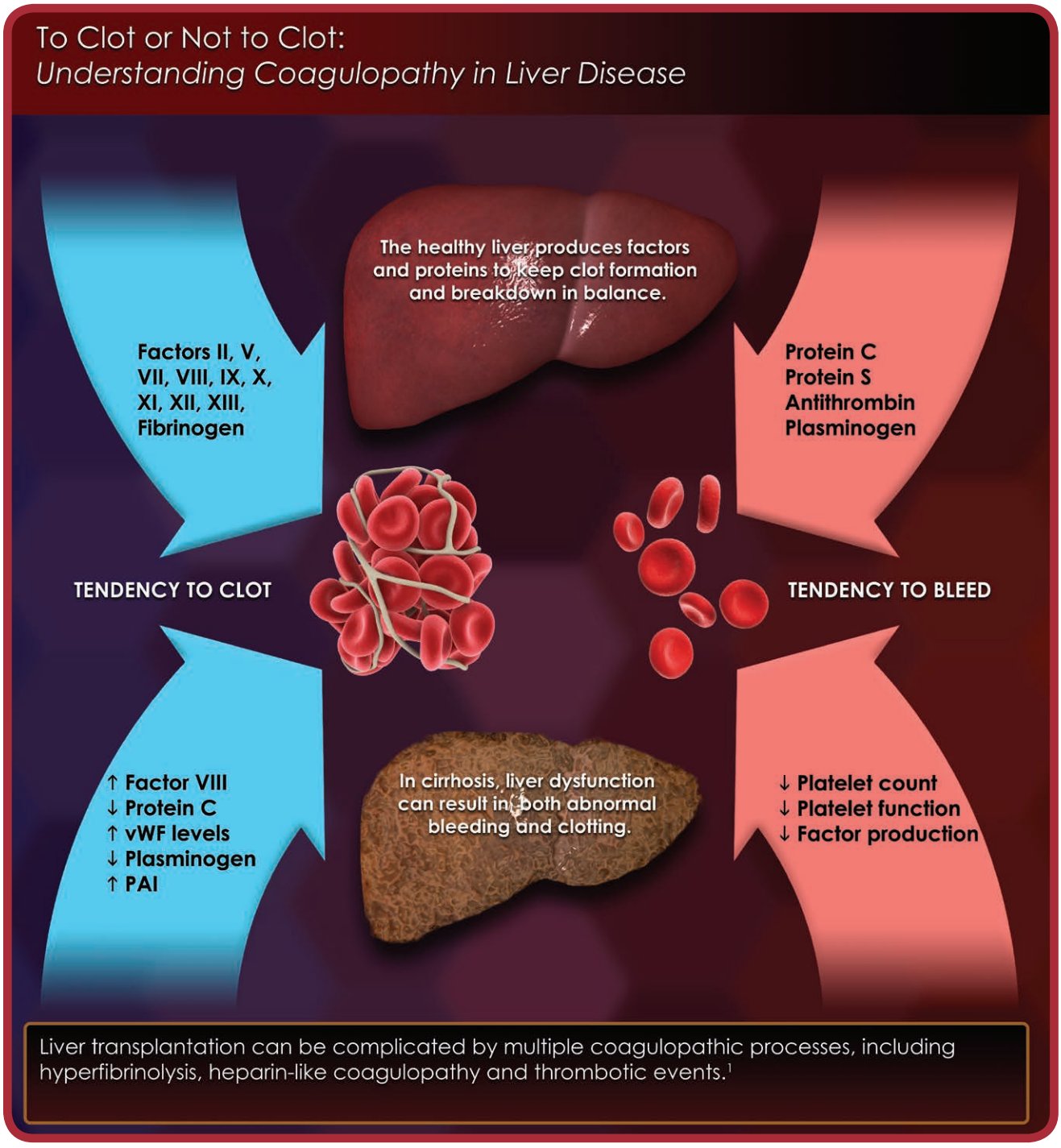

One of the hallmarks of end-stage liver disease is the manifestation of coagulopathy induced by a change in normal liver function, which disrupts the careful balance between bleeding and clotting. This can induce a physiological state where a patient is prone to abnormal bleeding, abnormal clotting, or both of those states together. In this infographic, we review the function of the normal liver in maintaining hemostasis and describe some of the physiological dysfunction that can be induced by end-stage liver disease.

PAI indicates plasminogen activator inhibitors; vWF, von Willebrand factor.

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REFERENCE

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NARRATIVE REVIEW ARTICLE

The Coagulation Profile of End-Stage Liver Disease and Considerations for Intraoperative Management

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The coagulopathy of end-stage liver disease results from a complex derangement in both anticoagulant and procoagulant processes. With even minor insults, cirrhotic patients experience either inappropriate bleeding or clotting, or even both simultaneously. The various phases of liver transplantation along with fluid and blood product administration may contribute to additional disturbances in coagulation. Thus, anesthetic management of patients undergoing liver transplantation to improve hemostasis and avoid inappropriate thrombosis in the perioperative environment can be challenging. To add to this challenge, traditional laboratory tests of coagulation are difficult to interpret in patients with end-stage liver disease. Viscoelastic coagulation tests such as thromboelastography (Haemonetics Corporation, Braintree, MA) and rotational thromboelastometry (TEM International, Munich, Germany) have helped to reduce transfusion of allogeneic blood products, especially fresh frozen plasma, but have also lead to the increased use of fibrinogen-containing products. In general, advancements in surgical techniques and anesthetic management have led to significant reduction in blood transfusion requirements during liver transplantation. Targeted transfusion protocols and pharmacologic prevention of fibrinolysis may further aid in the management of the complex coagulopathy of end-stage liver disease. (Anesth Analg 2018;126:46–61)

Historically, the coagulopathy of end-stage liver disease has been characterized as a paucity of coagulation factors, with treatment generally focusing on the replacement of these factors through fresh frozen plasma (FFP) administration. The coagulopathy of liver disease is increasingly recognized to be much more complicated than simply a decrease in coagulation factors produced by the liver as there are major derangements in both anticoagulant and procoagulant processes in the cirrhotic patient. Thus, treatment of these patients is complex and requires understanding of these pathophysiologic processes. For added complexity, the various causes of liver disease, and importantly the rate at which liver disease develops (eg, acute versus chronic liver failure), also affect each cirrhotic patient's hemostatic profile.

Normal hemostasis results from the complex interaction between platelets, coagulation factors, and disrupted endothelium at the site of vascular injury. It concludes in thrombin-mediated conversion of fibrinogen to fibrin at the site of injury (Figure 1). The ensuing dissolution of the clot through fibrinolysis is initiated by plasmin, which degrades the fibrin molecules that previously stabilized the clot. Fibrinolysis is crucial in preventing excessive clot formation. The function of all 3 major components of the coagulation process (platelets, coagulation factors, and fibrinolysis) is markedly disturbed in the cirrhotic patient. Such significant derangements leave the cirrhotic patient in a tenuous state with a propensity toward either major bleeding or major clotting, or at times even both, in response to even minor insults to their system. These derangements have major implications for the anesthesiologist caring for patients with end-stage liver disease, particularly during liver transplantation. This review will examine the pathophysiology of deranged hemostasis in end-stage liver disease, difficulties with evaluation of the coagulation system in patients with liver disease, and management of blood loss and blood transfusion during liver transplantation.

COAGULOPATHY OF END-STAGE LIVER DISEASE: AN IMBALANCE OF CLOTTING AND BLEEDING

Alterations in both the quantity and quality of platelets and many of the coagulation factors produced by the liver (procoagulant factors such as factors II, V, VII, VIII, X, XI, XII, XIII, and fibrinogen and anticoagulant factors such as antithrombin, protein C, and protein S) lead to a propensity for bleeding and simultaneous thrombosis in patients with end-stage liver disease. Perturbations occurring in both pro- and anticoagulant processes explain the complex coagulation profile of these patients and require careful consideration.

Platelets

Under normal conditions (Figure 1), platelet aggregation is stimulated by exposure of von Willebrand factor (vWF) and collagen in the vascular wall, both of which are normally shielded and inhibited by intact endothelium. When platelets become activated by exposed vWF and collagen, the subsequent interaction with vWF, alteration in platelet morphology, and release of mediators such as adenosine diphosphate and thromboxane A_2 cause the platelets to aggregate.[1] Concurrently, activation of the coagulation cascade leads to the formation of thrombin,

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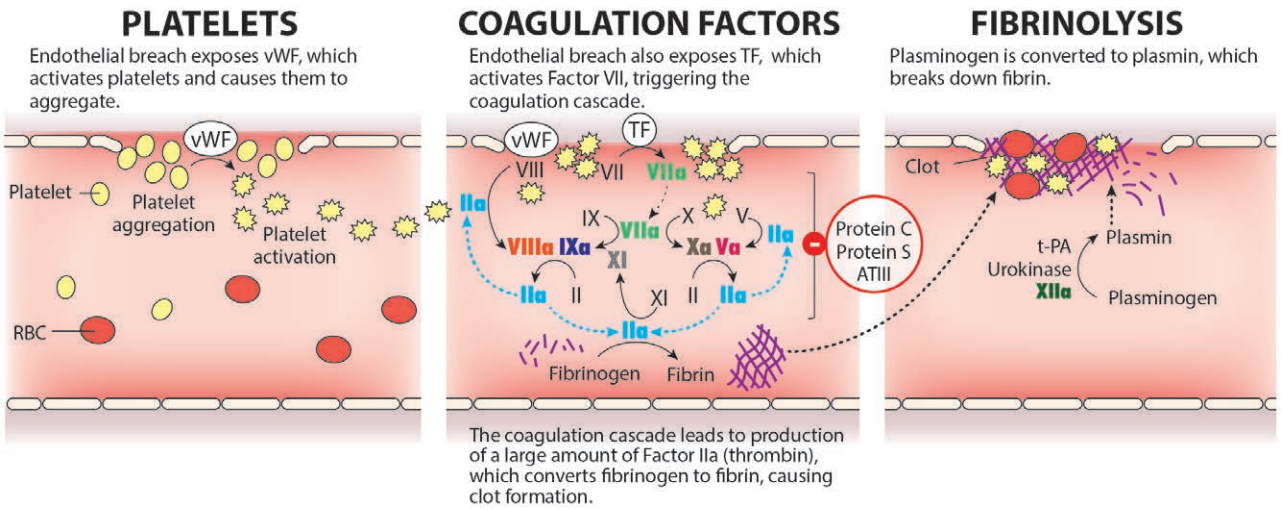

Figure 1. The normal coagulation process. The liver produces multiple proteins involved in the normal clotting process including coagulation factors, fibrinogen, and plasminogen. Exposure of vWF from an endothelial breach activates platelets leading to platelet aggregation. The endothelial breach also exposes TF and collagen and results in binding of factor VII and subsequent activation of the coagulation cascade. Activation of the coagulation cascade leads to factor IIa (thrombin) production, which converts fibrinogen to fibrin. Fibrin polymerizes to form a fibrin mesh and stabilizes the clot. Finally, plasminogen is converted to plasmin by factor XIIa, t-PA, and urokinase. Plasmin degrades fibrin, thereby leading to clot breakdown. ATIII indicates antithrombin III; TF, tissue factor; t-PA, tissue plasminogen activator; RBC, red blood cell; vWF, von Willebrand factor.

which converts fibrinogen to fibrin. Fibrin cross-links to form an insoluble mesh over the aggregated platelets, thus stabilizing the clot at the site of endothelial injury.[1,2]

Thrombocytopenia is commonly encountered in patients with end-stage liver disease and is thought to develop from congestive splenomegaly due to portal hypertension.[3] Platelet counts often fall within the range of 30 to 100 × 10^9/L. In addition to a quantitative platelet deficiency, platelets are also functionally altered due to increased endothelial production of nitric oxide and prostacyclin (Figure 2).[4–7] Nitric oxide and prostacyclin typically are released from intact endothelium and act as inhibitors of platelet activation. Thus, increased production of these mediators further serves to inhibit clot formation by platelets in patients with cirrhosis.[8]

In addition to thrombocytopenia and platelet dysfunction increasing the risk of bleeding, other platelet alterations contribute to risk of inappropriate clotting. Levels of a plasma metalloproteinase produced in the liver termed a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) are decreased as a result of liver disease. ADAMTS13 normally acts to cleave the bound platelet-vWF. Thus, as a result of decreased ADAMTS13, levels of ultralarge vWF are increased, which helps stimulate platelet aggregation. These alterations help normalize platelet function in cirrhotic patients.[7,9] Without the reduced expression of ADAMTS13, platelet dysfunction would likely be much worse in cirrhotic patients.

Although elevations in vWF should theoretically help restore more normal platelet function, recent evidence suggests that higher levels of vWF are associated with worse outcomes in patients with end-stage liver disease.[10–12] Using vWF as a marker of endothelial function, abnormally high levels suggest activation of the endothelium and thus a propensity toward a prothrombotic state.[11] Endothelial dysfunction may play a role in the increased need for transjugular intrahepatic portosystemic shunt placement, increased incidence of liver transplantation, and decreased survival demonstrated in cirrhotic patients with high levels of circulating vWF.[11]

Coagulation Factors

In the setting of normal coagulation and health, the liver produces both procoagulant factors II, V, VII, VIII, X, XI, XII, XIII and fibrinogen and anticoagulant factors such as antithrombin, proteins C and S (Figure 1).[13] The majority of pro- and anticoagulant factors are markedly decreased in chronic liver disease due to decreased synthetic function by the cirrhotic liver (Figure 2). Factor VIII is produced mainly by the sinusoidal cells of the liver, with minor contributions by the lung, endothelial cells, and spleen.[14] Levels of procoagulant factor VIII, however, are markedly increased in patients with cirrhosis. This increase in factor VIII is attributed to increased levels of vWF, as vWF binds factor VIII and thereby protects it from cleavage by plasma proteases.[2,15] Elevation in activated factor VIII leads to generation of thrombin and has been associated with an increased incidence of venous thromboembolism.[16] Further, thrombin activates factor VIII[17] and factor VIII is modified by several of the serine proteases in the coagulation system.[18] Analysis of the serum from 134 cirrhotic patients revealed not only increased levels of factor VIII but also both decreased levels of protein C and resistance to the action of thrombomodulin (a cofactor in the thrombin-mediated activation of protein C) resulting in a hypercoagulable state.[19] As the severity of cirrhosis progresses, these changes are amplified and seem to produce a greater degree of hypercoagulability in patients with Child-Pugh class C cirrhosis as compared to class A or B patients.[19]

Fibrinogen, a key coagulation protein made up of 6 polypeptide chains, is normally produced in hepatocytes.[20,21] In the setting of normal coagulation function, fibrinogen is cleaved by the protease thrombin to form fibrin molecules that polymerize, contributing to clot stabilization by cross-linking–activated platelets. Patients with end-stage liver disease may have a reduced amount of fibrinogen, particularly

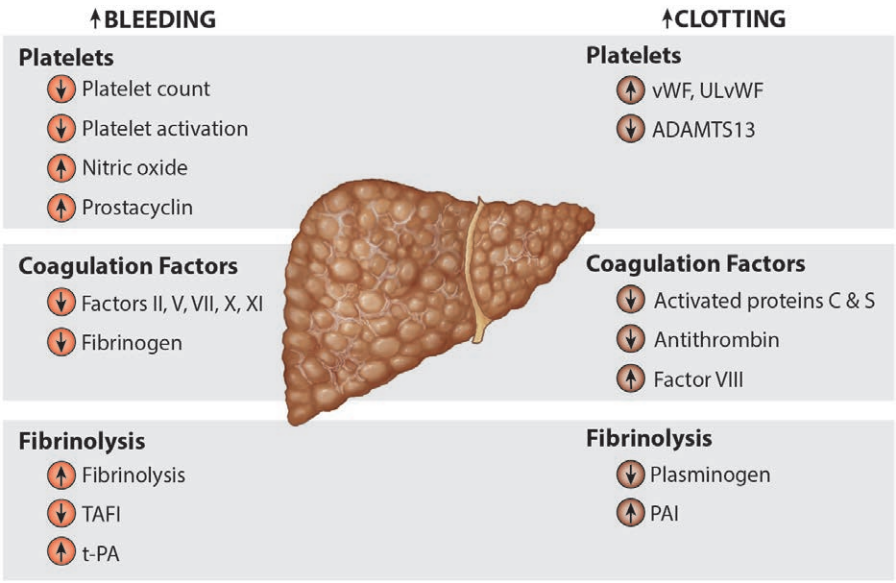

Figure 2. The coagulopathy of liver disease. The coagulopathy of liver disease involves derangements in both antithrombotic and prothrombotic processes. Alterations in cirrhotic patients that lead to increased bleeding include decreased quantity of platelets, coagulation factors (factors II, V, VII, X, and XI), and fibrinogen. Additionally, increased production of nitric oxide and prostacyclin in liver disease causes decreased platelet activation. Fibrinolysis is also increased, which further promotes bleeding. Prothrombotic alterations in these patients include decreased activated proteins C and S, antithrombin, and plasminogen. Decreased plasminogen counteracts the increase in fibrinolysis. Decreased ADAMTS13 and increased vWF, ULvWF, and factor VIII all serve to restore normal platelet function. Due to these many alterations, even minor insults to patients with liver disease can cause significant bleeding or clotting. ADAMTS13 indicates a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; PAI, plasminogen activator inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; t-PA, tissue plasminogen activator; ULvWF, ultralarge von Willebrand factor; vWF, von Willebrand factor.

patients with severe cirrhosis and acute liver failure, and may also have dysfibrinogenemia or functionally abnormal fibrinogen.[22,23] Fibrinogen levels are not always decreased, as illustrated by frequently normal levels of fibrinogen in patients with mild to moderate cirrhosis. In fact, patients with mild to moderate cirrhosis may actually have elevated levels of fibrinogen as it is an acute phase reactant.[24,25] One study comparing fibrinogen levels in patients with cirrhosis reported that the median fibrinogen level for patients without cirrhosis was 1.8 g/L, whereas the median fibrinogen level for cirrhotic patients in Child-Pugh class A was 2.1 g/L, in Child-Pugh class B was 2.4 g/L, and in Child-Pugh class C was 1.3 g/L.[26] The dysfibrinogenemia of advanced liver disease has been attributed to an increased number of sialic acid residues on the fibrinogen molecule, which impairs fibrin molecule polymerization and, thus, clot stabilization.[24,27]

Due to all of these alterations, it may seem that there has been a balanced reduction of both pro- and anticoagulant factors resulting in normal hemostasis (Figure 2).[2,28] Indeed, early in the course of liver disease, patients may appear to have normal coagulation function. However, it is more likely that these parallel deficiencies in pro- and anticoagulant pathways have not yet reached clinical significance and many of the pathologic changes are invisible. This has clinical importance as these complex derangements in hemostasis affect the ability to make predictions of bleeding versus clotting using a limited set of laboratory tests as discussed below.

Fibrinolysis

The final phase of the coagulation process, which is also disordered in liver disease, is the dissolution of a clot through fibrinolysis. Initiation of fibrinolysis relies on the conversion of plasminogen to plasmin, which degrades fibrin and destabilizes the clot (Figure 1). Conversion of plasminogen to plasmin is activated by factor XIIa, tissue plasminogen activator (t-PA), and urokinase plasminogen activator.[2] Prevention of fibrinolysis, on the other hand, depends partly on thrombin-activatable fibrinolysis inhibitor (TAFI).[2] The thrombin–thrombomodulin complex is responsible not only for activating protein C[29] but also converts TAFI to its active form (TAFIa), which inhibits the conversion of plasminogen to plasmin.[30] TAFI levels are generally decreased in patients with end-stage liver disease, often in proportion to the severity of the disease due to decreased synthesis by the liver. As with platelets, these activators and inhibitors of fibrinolysis are abnormal in the setting of end-stage liver disease, which contributes to a state of hyperfibrinolysis with the concomitant risk of increased clinical bleeding.[3,30,31] However, 2 studies in acute and decompensated chronic liver disease have shown a normal fibrin hemostasis state, as measured by thromboelastography (TEG), despite involving critically ill patients with acute liver failure and infection, respectively.[32,33] The lack of hyperfibrinolysis, or even potential propensity for hypofibrinolysis (with risk of thrombosis), is thought to be due to increased levels of plasminogen activator inhibitor (PAI) and decreased levels of plasminogen in patients with end-stage liver disease.[2] Therefore, the degree to which a potential derangement in fibrinolysis in cirrhotic patients contributes to clinically significant bleeding remains unclear.

PROBLEMS WITH TRADITIONAL LABORATORY TESTS

All of the derangements described above interact in a complex manner to simultaneously tip the scale toward both

thrombosis and bleeding. While the increased risk of bleeding in cirrhotic patients has long been the center of attention, it is important to remember that these patients are also at risk for serious thrombotic events both in the peripheral and portal venous systems.[2,3,34] In the inpatient hospital setting, a large-scale, multivariate, multicenter analysis identified that chronic liver disease remains a risk factor for venous thromboembolism when compared to patients without liver disease.[35] Furthermore clinically significant rates of venous thromboembolism up to 6.3% have been noted in patients hospitalized with cirrhosis, indicating that these patients are not, as once thought, "autoanticoagulated."[36,37]

Thus, determining ways to accurately and, particularly in the operating room, quickly identify whether a patient with liver disease is at increased risk of bleeding or clotting is important when attempting to treat their underlying disorder.

Misled by INR

It has long been assumed that because the traditional laboratory tests of coagulation, such as prothrombin time (PT) and international normalized ratio (INR), are commonly abnormal in patients with liver disease, this must directly correlate with increased risk for significant bleeding in the cirrhotic patient. However, this assumed correlation has not been proven despite significant research.[38]

It is important to remember that the INR laboratory test was initially developed to aid in titration of oral anticoagulant regimens rather than to predict propensity for bleeding.[39] Thus, the laboratory value can be misleading. In fact, depending on the specific thromboplastin assay used, the PT and INR values reported from the same patient sample can vary widely (mean difference of 4.8 points on INR scale between highest and lowest of the samples).[40,41] This is particularly concerning as the model of end-stage liver disease (MELD) score used in organ allocation relies, in part, on the patient's INR value. The interlaboratory variation is common because the INR is not standardized to a population of patients with liver disease, instead those on oral anticoagulation (such as warfarin) who have a significantly different coagulation profile compared with patients with liver disease.[19,42] To correct for the phenomenon, a variety of methods have been suggested including a liver disease–specific reference thromboplastin to interpret PT/INR in this population.[41,42]

If INR values were truly correlated with the cirrhotic patient's bleeding risk, increased blood product use would be expected during liver transplantation in patients with higher preoperative INR. However, the power of preoperative INR to predict blood loss and transfusion requirements is variable and most studies evaluating transfusion requirements are limited by their retrospective nature. Table 1 reviews multiple studies that attempted to evaluate the role of preoperative INR in predicting perioperative transfusion requirements.[43–51] Despite the identification of multiple factors associated with increased transfusion requirements

Table 1. Studies Evaluating the Role of INR in Predicting Perioperative Blood Transfusions

Researchers	Sample Size	Patient Characteristics	Main Outcome
Massicotte et al (2004)[43]	206	Consecutive liver transplants (Jan 1998–Apr 2002); average MELD 18.3.	INR, platelet count, and duration of surgery all independent predictors for transfusion of >4 units pRBCs; large interprovider variability.
McCluskey et al (2006)[44]	460	Consecutive liver transplants (Jan 1998–Mar 2004); only 1 transplant per patient included during this time period; average MELD 15.9.	INR >2.0 predicted the need for >6 units pRBCs in 24 h.
Frasco et al (2005)[45]	96 (27 living donor, 69 cadaveric donor)	Primary liver transplants (Apr 2001–Mar 2004); average MELD living donor 13.2 and cadaveric donor 22.8.	INR associated with amount of FFP (but not pRBCs) transfused.
Steib et al (2001)[46]	410	Consecutive liver transplants (Jan 1988–Dec 1998); average MELD not reported.	Decreased PT (reported as % of normal PT value) associated with high blood loss group (patients requiring ≥12 units of pRBCs), although not predictive.
Cacciarelli et al (1996)[47]	306	Primary liver transplants (Jan 1992–Dec 1994); 48% of group requiring no pRBCs were Modified Child's Class C compared with 73% of group requiring ≥1 unit of pRBCs.	Higher PT associated with group requiring ≥1 unit of pRBCs, although not predictive.
Massicotte et al (2008)[48]	200	Consecutive liver transplants (Jan 2002–Dec 2005); average MELD 19.	No significant difference in units of pRBCs transfused, blood loss (mL), or final Hgb between patients with preoperative INR <1.5 and preoperative INR ≥1.5.
Findlay and Rettke (2000)[49]	583	Consecutive liver transplants (Jun 1986–Nov 1995); average MELD not reported.	No significant association between preoperative INR and intraoperative blood transfusion requirement.
Modanlou et al (2009)[50]	126	Primary liver transplants (Jan 2004–Dec 2006); average MELD 18.	No significant difference between preoperative INR and patients requiring ≤10 units pRBCs or >10 units pRBCs.
Cywinski et al (2014)[51]	804	Primary cadaveric liver transplants (Jan 2001–Jun 2010); average MELD 21.	Higher pretransplant INR associated with increased pRBC transfusions and cell-saver use but unreliable predictive power.

Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio; MELD, model of end-stage liver disease; pRBC, packed red blood cell; PT, prothrombin time.

during liver transplantation (including pretransplant INR in many of the studies), researchers have been unable to develop an algorithm to reliably predict intraoperative transfusion requirements using available preoperative laboratory data. Findlay and Rettke[49] concluded that the largest source of variability in transfusion requirements is related to intraoperative and surgical factors, and that preoperative variables including age, creatinine, bilirubin, encephalopathy, platelet count, and pulmonary artery pressures are poor predictors for intraoperative transfusion requirements.

While increased INR is indeed statistically associated with increased transfusion requirements, it explains only a small portion of the variability in intraoperative blood product requirements. Ultimately, as highlighted in the editorial of Cywinski et al's[51] work, the challenge remains to accurately predict which liver transplant patients will require the greatest amount of blood products.[52] As a result, many centers prepare for massive transfusion for most patients undergoing liver transplantation; thus, the anesthesiologist must be prepared for all liver transplant patients to require significant blood transfusion.[52] Nonetheless, new ways of measuring and predicting profound coagulopathy and blood loss in liver transplant patients should continue to be explored. Toward that effort, a recently published study describes a reliable model to identify patients at high risk for massive transfusion using the MELD score, and included whether the patient was undergoing simultaneous liver and kidney transplant, cirrhosis stage, hemoglobin concentration, platelet concentration, and—instead of traditional measures of coagulation—viscoelastic coagulation measures (TEG R interval and angle).[53] Whether or not this model is generalizable beyond the authors' institution is unknown. Such alternative measures of coagulation and their applicability in cirrhotic patients will be discussed in the next section.

Alternative Measures of Coagulation

TEG and rotational thromboelastometry (ROTEM) are coagulation tests used to assess functional coagulation (or the strength of clot formation) in the perioperative period.[54] These tests allow for real-time viscoelastic measurements to determine the time to clot formation, firmness of the clot, and time to clot dissolution. Characteristic results of these measures help identify different coagulation defects including hyperfibrinolysis, hypofibrinogenemia, thrombocytopenia, and a hypercoagulable state. While TEG and ROTEM results are generally considered equivalent measures of viscoelastic coagulation parameters, important differences exist between the 2 tests with the potential for altering transfusion decisions depending on the test used.[55,56] Importantly, different coagulation activating agents are used for each of the tests. Kaolin is used as the activating agent in the standard TEG assay (k-TEG) while the activators used for ROTEM assays are tissue factor when measuring the extrinsic coagulation pathway (EXTEM) and ellagic acid when measuring the intrinsic coagulation pathway (INTEM).[57] Kaolin is also used as the activating agent for activated partial thromboplastin time (aPTT), a traditional coagulation measure that has not been shown to correlate well with the coagulation status of patients with end-stage liver disease.[58] Rapid TEG, with the addition of tissue factor as an activating agent with kaolin, and functional fibrinogen TEG are alternative TEG assays that have been evaluated in liver transplantation and may help guide transfusion.[59] Nevertheless, both TEG and ROTEM results can guide the clinician in appropriate blood transfusion therapy and minimize risks from unnecessary blood product administration.

TEG and ROTEM are frequently used to measure the coagulation function of cirrhotic patients during liver transplant surgery. The results of these tests can help identify pretransplant coagulopathy, as well as dilutional coagulopathy, hypofibrinogenemia, or hyperfibrinolysis during the course of surgery (Figure 3).[60–62] Additionally, changes in coagulation during the various phases of the liver transplantation surgery itself may also help guide blood transfusion therapy (Figures 4 and 5). It is important to recognize that the viscoelastic coagulation assays have differing sensitivities for detecting hyperfibrinolysis. In a study comparing the ability of TEG and ROTEM measures to accurately identify hyperfibrinolysis, 89 of 250 total measurement points during 37 liver transplantations demonstrated hyperfibrinolysis (as confirmed by APTEM, an EXTEM-based assay with added aprotinin), 94% of which were detected by FIBTEM (an EXTEM-based assay measuring the fibrin portion of the clot), 46% by EXTEM, and only 24% by k-TEG.[63] Thus, FIBTEM was the most sensitive viscoelastic coagulation measure for

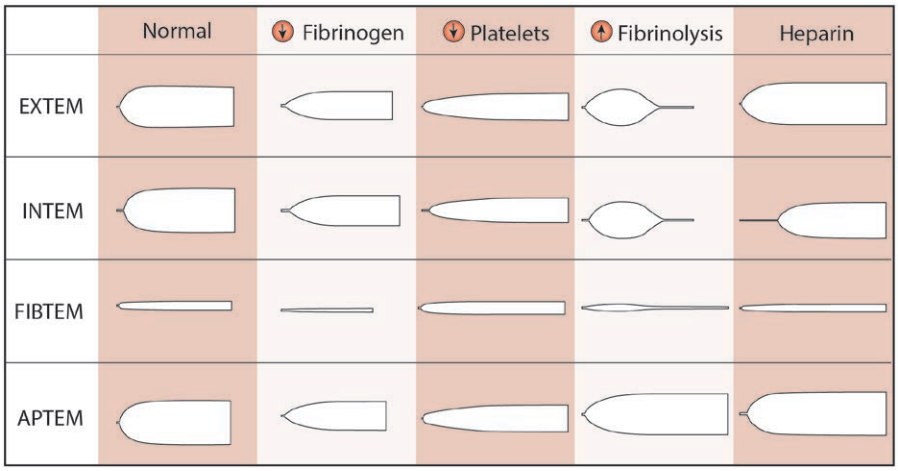

Figure 3. Rotational thromboelastometry in normal and abnormal states. Typical tracings seen in the various ROTEM channels such as EXTEM, INTEM, FIBTEM, and APTEM. Normal viscoelastic testing is shown for comparison along with typical tracings for hypofibrinogenemia, thrombocytopenia, hyperfibrinolysis, and heparin effect. APTEM indicates with aprotinin added to evaluate for hyperfibrinolysis; EXTEM, extrinsic coagulation pathway; FIBTEM, fibrinogen contribution; INTEM, intrinsic coagulation pathway; ROTEM, rotational thromboelastometry.

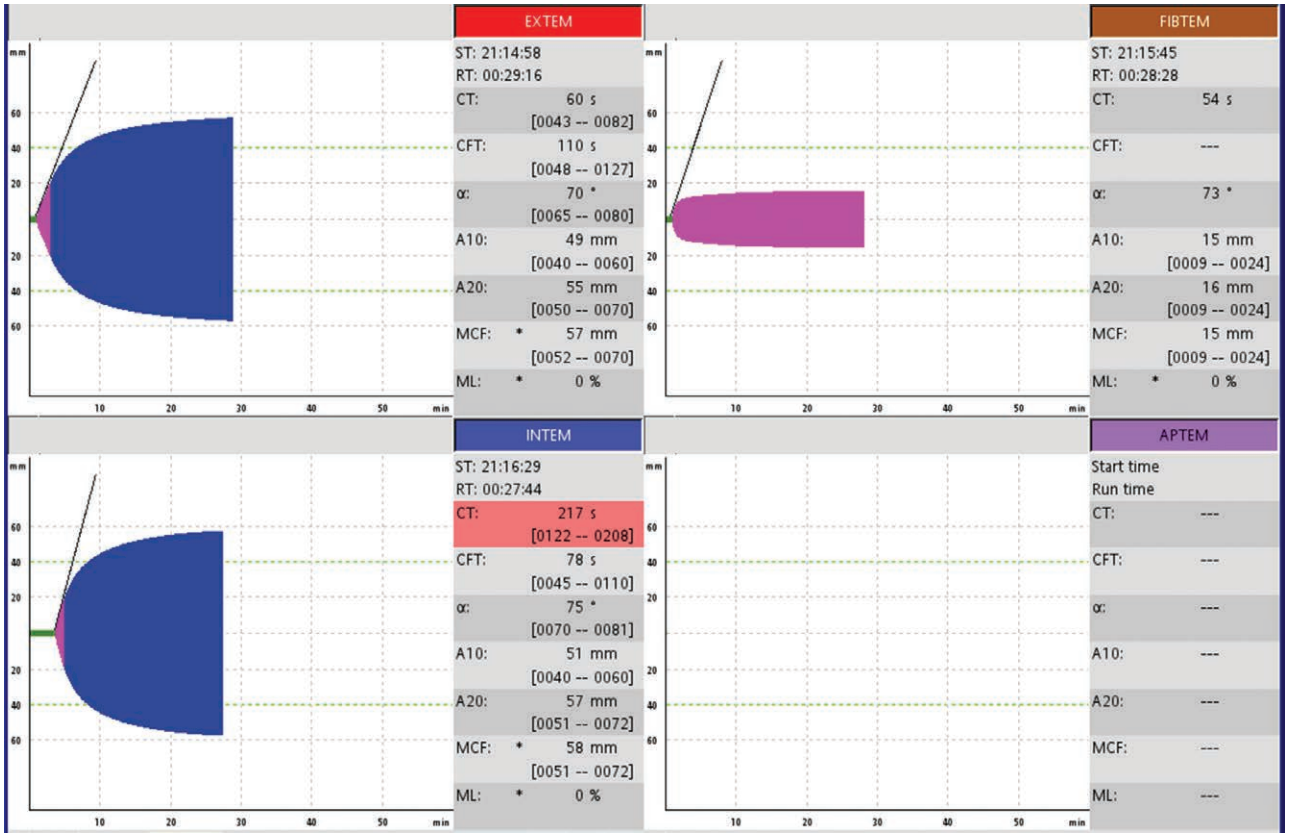

Figure 4. Rotational thromboelastometry in nonbleeding liver transplant patient. ROTEM tracings illustrate normal MCF on EXTEM, INTEM, and FIBTEM in a patient undergoing liver transplantation at the start of surgery. CFT indicates clot formation time; CT, clotting time; EXTEM, extrinsic coagulation pathway; FIBTEM, fibrinogen contribution; INTEM, intrinsic coagulation pathway; MCF, maximum clot firmness; ML, maximum lysis; ROTEM, rotational thromboelastometry.

detection of hyperfibrinolysis, which is likely due to its ability to isolate the contribution of fibrinogen to clot formation with use of a platelet inhibitor (cytochalasin D).

Table 2 reviews multiple studies evaluating the effect of using viscoelastic coagulation tests (TEG and ROTEM) during liver transplantation on perioperative blood product transfusions.[64–68] Overall, these studies suggest that transfusion protocols based on TEG and ROTEM lead to reduced transfusion, yet no survival benefit has been observed to date. Indeed a Cochrane review emphasized that many of the studies available were of limited power and at high risk of bias.[69] Thus, while TEG and ROTEM are seemingly superior tests of coagulation function in cirrhotic patients undergoing liver transplantation compared with traditional measures, more research into both short- and long-term outcomes should be explored. Additionally, it remains unclear whether the use of these tests in selected patients with end-stage liver disease or during specific times during the course of the surgery would be of additional outcome benefit.

COAGULOPATHY AND ITS ASSESSMENT DURING LIVER TRANSPLANTATION

It is important to differentiate the coagulopathy that characterizes cirrhosis in general from that which presents at different stages of both liver transplantation and nonhepatic surgeries. The coagulopathy present at the beginning of any surgery for a patient with cirrhosis relates to the underlying pathophysiology of end-stage liver disease. However, as liver surgery proceeds with dissection of the diseased liver and fluid and blood product therapy begins, a de novo coagulopathy, dilutional in origin, often results.[31] During the anhepatic phase of liver transplantation, there is absence of synthetic activity from the diseased liver so any hepatically produced clotting factors come only from transfused blood product, with loss through consumptive processes.[70] After reperfusion of the transplanted allograft, clotting factors may be produced and secreted by the new liver as long as it has adequate perfusion pressure and oxygen supply; however, the allograft may also release toxins that accumulated during the ischemic period.[71] The combined consequences of ischemia and the underlying coagulopathy merge at reperfusion, often leading to a period of hemostatic instability and increased bleeding. Once the transplanted liver begins to synthesize coagulation factors and detoxifies accumulated toxins and metabolites from the anhepatic phase, and acid-base balance is restored, coagulation typically improves.

Hyperfibrinolysis

A degree of dysregulation of normal fibrin physiology is often present in patients with cirrhosis and is commonly discovered preoperatively in patients presenting for liver transplantation.[72] Kang et al[73] found a whole blood clot lysis index <80% (suggesting hyperfibrinolysis) in 30.5% of liver transplant patients preoperatively. Further, 80% of these patients met the criteria for hyperfibrinolysis

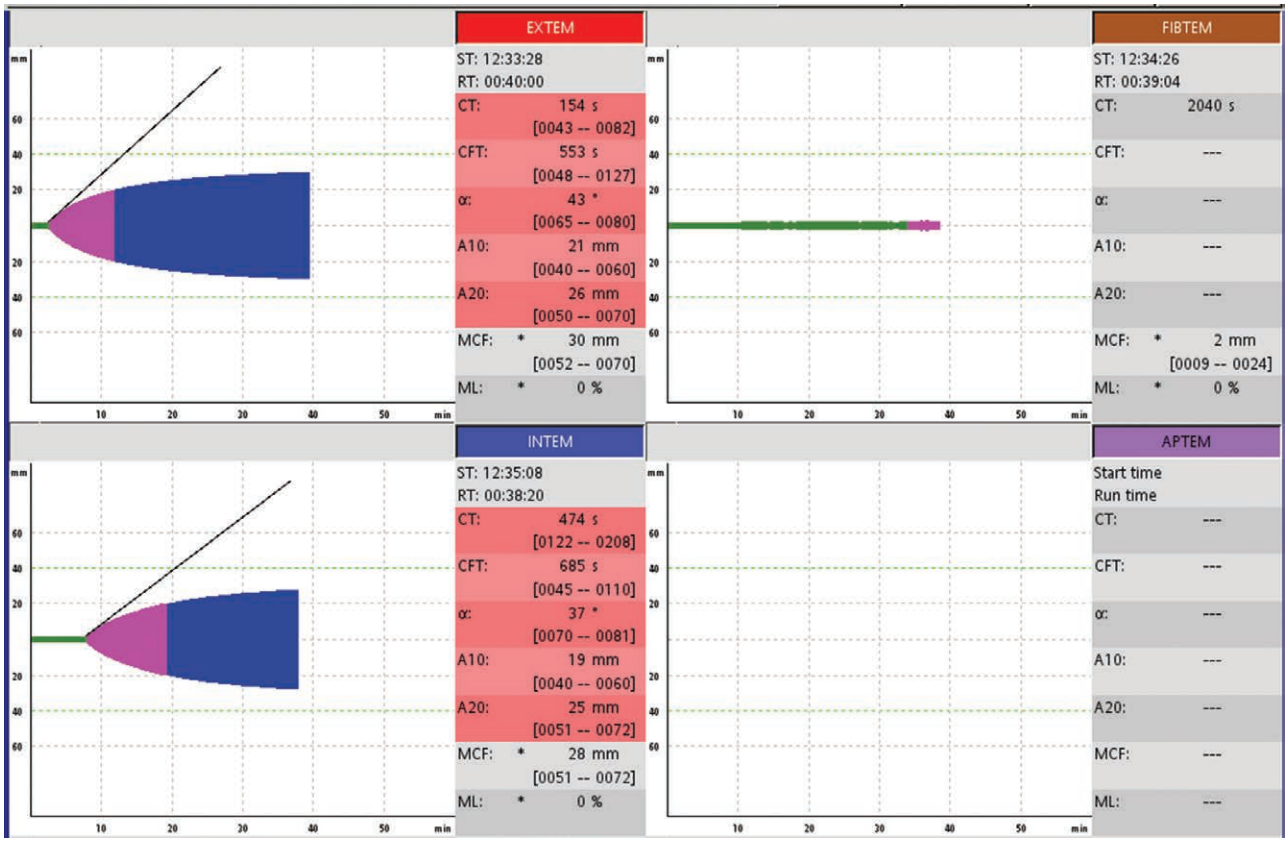

Figure 5. Rotational thromboelastometry in bleeding liver transplant patient. ROTEM tracings illustrate significantly reduced MCF on EXTEM, INTEM, and FIBTEM in a patient who has hemorrhage requiring massive transfusion during liver transplant surgery with requirement for coagulation factor replacement via fresh frozen plasma, fibrinogen replacement with cryoprecipitate, and platelet transfusion for reduced clot strength and thrombocytopenia. CFT indicates clot formation time; CT, clotting time; EXTEM, extrinsic coagulation pathway; FIBTEM, fibrinogen contribution; INTEM, intrinsic coagulation pathway; MCF, maximum clot firmness; ML, maximum lysis; ROTEM, rotational thromboelastometry.

intraoperatively (either with a whole blood clot lysis index <80% or clot lysis time <180 minutes), occurring most commonly during reperfusion.[73] Steib et al[74] compared multiple baseline coagulation parameters of 56 cirrhotic patients undergoing liver transplantation and later compared the baseline values in the group of patients who developed hyperfibrinolysis intraoperatively with the patients who did not experience this complication. They found 100% sensitivity for predicting increased intraoperative blood loss and hyperfibrinolysis in patients with both a preoperative maximum amplitude (MA) on TEG ≤35 mm and serum fibrinogen degradation product values >48 mg/L.[74]

Hyperfibrinolysis in the cirrhotic patient population has been attributed to changes in t-PA, PAI, and TAFI activity.[75,76] Such changes are dynamic throughout liver transplantation surgery, with a steady rise in t-PA throughout the anhepatic period when clearance by the liver is unavailable, and another significant increase at reperfusion.[75,77] PAI displays the opposite pattern (decreased levels during the anhepatic phase and reperfusion), which together helps explain why fibrinolysis may occur after reperfusion and usually corrects spontaneously as the liver graft begins to function.[75,78] This phenomenon has been mathematically modeled, with the conclusion that the observed changes in t-PA in the anhepatic phase are a function of both preoperative levels and surgical blood loss acting as an alternate clearance mechanism.[79] The variable degree of hyperfibrinolysis may also reflect certain organ or donor factors. In a porcine model, Porte et al[71] demonstrated significantly increased fibrinolysis and decreased platelets in the liver outflow blood (compared with systemic blood) after reperfusion, suggesting the new graft plays a role in postreperfusion coagulopathy. Cirrhotic patients also have decreased TAFI levels, which has not only been correlated with hyperfibrinolysis[30] but also with increased mortality over a 3-year period in cirrhotic patients with the lowest TAFI levels.[80]

Heparin-Like Coagulopathy

A second common contributor to bleeding during liver transplantation is a heparin-like coagulopathy. This phenomenon, demonstrated in characteristic TEG evaluation of clot strength and alteration of the underlying profile in vitro with exogenous heparinase (either to normality or a different abnormal profile), is variably reported particularly during the postreperfusion stage of liver transplantation leading to speculation that it is due to residual or accumulated heparin from the graft.[81–84] At the time of arterial cross-clamp during the donor hepatectomy, heparin is administered systemically and then the liver graft is flushed with University of Wisconsin solution without anticoagulants.[81] During reperfusion, previously administered heparin to the donor can be released into the recipient circulation. Endogenous and exogenous heparanoids are eliminated by the liver, thus with end-stage liver disease

Table 2. Studies Evaluating Effect of Using of Viscoelastic Coagulation Tests on Perioperative Blood Product Transfusions

Researchers	Sample Size	Patient Characteristics	Coagulation Test Used	Main Outcome
Wang et al (2010)[64]	28	Consecutive liver transplants (Jan 2005–Dec 2006); average MELD 11.6 in control group and 11.0 in TEG group.	Randomized to protocols guided by TEG versus standard measures (plt count, PT, aPTT, fibrinogen).	TEG-guided transfusion protocol resulted in reduced FFP transfusions (12.8 vs 21.5 units), but no difference in 3-year survival.
Alamo et al (2013)[65]	303	Consecutive liver transplants; average MELD not reported.	Case–control; retrospectively compared cases with and without intraoperative ROTEM use.	Use of ROTEM intraoperatively decreased pRBC, FFP, and platelet transfusions in high risk patients (eg, MELD ≥21, retransplantation) and decreased postoperative complications.
De Pietri et al (2016)[66]	386	Consecutive liver transplants (Dec 2005–Dec 2014); average MELD 19.0 (prior to 2012) and 21.2 (2012–2014).	Cohort study; retrospectively compared a TEG-guided protocol with a newer TEG-guided protocol that included a FF-TEG test and fibrinogen concentrate administration.	Inclusion of FF-TEG test and fibrinogen concentrate use to a TEG-guided protocol decreased transfusion requirements of pRBCs, FFP, and platelets, but no difference in 30-day or 6-month survival; fibrinogen concentrate use increased.
Roullet et al (2015)[67]	60	Consecutive liver transplants (Jun 2012–Jun 2013); average MELD 17 (without group) and 20 (with group).	Prospective study; compared 30 patients first without use of a ROTEM-based algorithm, then 30 patients with the use of a ROTEM-based algorithm.	No difference in blood product transfusions; small, nonsignificant increased in fibrinogen concentrate use.
Fayed et al (2015)[68]	100	Living-donor liver transplants (Apr 2011–Sept 2012); average MELD 16.3.	Prospective study; preoperative ROTEM values compared with intraoperative blood transfusion requirements using univariate and multivariate linear regression analysis.	Many preoperative ROTEM values were predictive of transfusion requirements, most significantly for FFP.

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; FF-TEG, fibrinogen functional thromboelastography; MELD, model of end-stage liver disease; pRBC, packed red blood cell; PT, prothrombin time.

and a newly reperfused liver, this heparin-like coagulopathy may contribute to bleeding. Indeed heparin-like coagulopathy is present at the beginning of the transplant procedure in 31% of patients, increasing to approximately 75% immediately after reperfusion.[82] In hospitalized cirrhotic patients, the authors of a case–control study described a correlation of heparin-like coagulopathy with the presence of concomitant systemic infection, speculating that infection was the initiating factor in the observed coagulopathy.[85]

Thromboembolic Events

In contrast to the aforementioned coagulopathy that may occur during liver transplantation and lead to clinically significant bleeding, it is crucial to recognize that potentially life-threatening thromboembolic events may also occur. For instance, pulmonary embolism and intracardiac thrombosis may occur during any phase of liver transplantation surgery, often leading to significant morbidity and mortality.[86] In fact, the incidence of pulmonary embolism during liver transplantation may be as high as 4%.[87] Thus, anesthesiologists must maintain a heightened level of awareness for the occurrence of significant thromboembolic events during liver transplantation. Use of ROTEM in the author's institution during liver transplantation (Figure 4) can help to identify not only patients at risk for bleeding but also those with normal viscoelastic measures of clot strength and fibrinogen contribution who may be at risk for thrombotic events throughout the dissection, anhepatic, reperfusion and postreperfusion phases of surgery.

While there is concern about bleeding at the time of reperfusion, there is also significant concern about thromboembolism as the liver graft is reperfused and clamps are removed from the hepatic artery, portal vein, and inferior vena cava. Thus, in some cases, intravenous heparin is administered to the recipient in order to prophylactically decrease the risk for thromboembolism. Nicolau-Raducu et al[88] found point-of-care Hepcon HMS plus kaolin-activated clotting time monitoring to be a reliable alternative to monitor the response to heparin as compared to laboratory-required anti-Xa assay for patients undergoing liver transplantation. However, shortly after reperfusion, Hepcon HMS plus was less consistent at picking up the additional heparin-like activity presumably from graft reperfusion.

Antiphospholipid antibody syndrome (APS) occurs as a result of autoantibodies that form to a variety of phospholipid binding proteins or the phospholipid in cell membranes. It is characterized as a hypercoagulable state with venous and arterial thrombosis, as well as mild to moderate thrombocytopenia. APS is diagnosed by demonstrating the presence of anticardiolipin antibodies of IgG or IgM subtypes or the presence of lupus anticoagulant.[89] Antiphospholipid antibodies have been noted in patients with liver disease such as primary biliary cirrhosis, autoimmune hepatitis, and chronic hepatitis C, and are more prevalent than in the general population.[90] Case reports of patients undergoing

liver transplantation have been published describing a type of catastrophic APS characterized by massive arterial and venous thromboses and multisystem organ failure.[89,91] Thus, for patients with antiphospholipid antibodies presenting for liver transplantation, suggested therapies include early anticoagulation, steroids, and preoperative plasmapheresis to reduce the antiphospholipid antibody titer prior to liver transplantation.[91] Monitoring the effect of heparin therapy in patients with APS is challenging as the lupus anticoagulant may prolong phospholipid-dependent coagulation tests such as the aPTT and the activated clotting time.[92] Typical management of the hypercoagulable state includes switching from unfractionated heparin to low molecular weight heparin.[92] If unfractionated heparin remains the best option to manage the risk for thrombosis in an APS patient, heparin antifactor Xa levels may be used to target appropriate anticoagulation.[92] Additionally, an individualized aPTT therapeutic range may be targeted to an aPTT goal 2 times the baseline aPTT.[92]

INTRAOPERATIVE MANAGEMENT OF HEMOSTASIS IN PATIENTS WITH CIRRHOSIS: MINIMIZING BLOOD LOSS AND TRANSFUSION REQUIREMENTS

Over the past 30 years, the overall volume of blood products transfused during liver transplantation has significantly decreased.[47,93,94] A recent study of 500 patients undergoing orthotopic liver transplantation reported zero packed red blood cell (pRBC) transfusions in 80% of cases.[95] This decline in blood transfusions during liver transplantation is likely due to many improvements in surgical and anesthetic techniques.[96,97] Nevertheless, large variations in transfusion practice between institutions (after accounting for blood loss) remain, suggesting a high degree of variability in transfusion of blood products as a response to bleeding in these patients.[98] Techniques for minimizing blood loss and blood product transfusion in patients with cirrhosis will be explored in this section.

Blood Product Use and Outcome

As transfusion requirements during liver transplantation have decreased, a significant difference has become apparent between outcomes of patients who require large transfusions of blood products and those that do not. Multiple authors have noted worse outcomes such as longer hospital stay, acute lung injury, and diminished survival demonstrated at various cutoff points between 6 or more units of pRBCs and 3 blood volumes of blood product.[99–102] Unfortunately, blood transfusion management is complicated by the inability to reliably predict preoperatively which patients will require large transfusions despite some factors having been identified as being associated with increased risk of transfusion such as preoperative anemia and age of the recipient.[51,103]

Increased morbidity and mortality have been associated with blood transfusion during liver transplant surgery. Patients undergoing liver transplantation who are more frequently transfused demonstrate increased risk of renal failure, hospital length of stay, and intensive care unit length of stay.[104–106] Additionally, de Boer et al[101] performed a retrospective analysis of 433 liver transplants between 1989 and 2004 and demonstrated a dose-dependent relationship between both the number of units of platelets and the number units of pRBCs transfused with 1-year survival. Further investigation into those patients who received platelet transfusions identified acute lung injury as the major cause of increased mortality.[107] Decreased survival was also shown in another large single-center retrospective analysis of 942 liver transplant patients in those patients who received 20 or more units of platelets.[106] Due to concern for the potential role of platelets in thrombotic events after reperfusion (such as hepatic artery thrombosis) and ischemia-reperfusion injury, many anesthesiologists choose to withhold platelet transfusions until there is significant clinical bleeding. Additionally, liver transplant anesthesiologists recognize that platelet count tends to rise once the new graft begins functioning. Some thresholds for platelet transfusion that have been described in various centers' blood transfusion algorithms during liver transplantation include: preoperative platelet count <50 g/L,[67] MA on TEG <55 mm,[64] MA on TEG <30 mm with MA on functional fibrinogen test (MA_{FFT}) >7 mm,[66] or EXTEM maximum clot firmness (MCF) <45 mm with a FIBTEM MCF >8 mm.[68] To date, there remains no definitive, evidence-based platelet count, or viscoelastic coagulation test measurement that serves as an absolute threshold for platelet transfusion during liver transplantation.

Thoughtful administration of blood component therapy is vital to minimize the adverse effects of blood transfusion. Heavy reliance on transfusion of FFP in response to elevated INR values in these patients has been a conventional component of treating coagulopathy in cirrhotic patients. However, hypofibrinogenemia and dysfibrinogenemia demonstrated in cirrhotic patients highlights the importance of cryoprecipitate (or fibrinogen concentrate, as available) administration to correct intraoperative coagulopathy. The fibrinogen level that defines hypofibrinogenemia in patients with end-stage liver disease remains unclear, particularly with the associated dysfibrinogenemia in this patient population. Generally, fibrinogen levels ≤1.0 g/L indicate a need for fibrinogen replacement, but in the setting of clinically significant bleeding, fibrinogen replacement may be considered for patients with fibrinogen levels <1.5 to 2.0 g/L.[108] Cryoprecipitate is prepared by thawing FFP, and the precipitated proteins form a gel-like fluid that is resuspended in a small amount of plasma. Cryoprecipitate is pooled in 4 to 6 unit aliquots and generally contains 15 g/L of fibrinogen,[109] whereas FFP contains a much lower concentration of fibrinogen (1–3 g/L)[108] and carries an increased risk of transfusion-related acute lung injury. Thus, while only 1.5 mL/kg of cryoprecipitate is required to increase plasma fibrinogen by 0.5 g/L, 15 mL/kg of FFP is needed to achieve the same effect.[110] Each cryoprecipitate concentrate prepared from 1 donor unit of plasma contains approximately 80–100 units of factor VIII, vWF, fibrinogen 150–300 mg, and factor XIII 40–60 units.[111] As prepared by a blood bank, a bag of cryoprecipitate for transfusion may be expected to raise the fibrinogen level by 30 mg/dL in a controlled situation.[111] In the setting of significant hemorrhage in a liver transplant patient with other transfusion requirements and fluid administration, there is a rather heterogeneous clinical

response of the fibrinogen level to cryoprecipitate transfusion. Thus more cryoprecipitate may be required than anticipated based on fibrinogen level or FIBTEM results on the ROTEM analysis. Plasma fibrinogen may be expected to increase by approximately 0.2375 g/L per 1 g of fibrinogen concentrate in surgical patients.[112]

Fibrinogen replacement with cryoprecipitate or fibrinogen concentrate has been shown to decrease surgical bleeding in general; additionally, administration can be guided by TEG or ROTEM results.[110] ROTEM FIBTEM cutoff levels of MCF 8 mm at 10 minutes have been shown to best predict the transfusion threshold for cryoprecipitate.[113] Figure 5 ROTEM tracings illustrate significantly reduced MCF on EXTEM, INTEM, and FIBTEM in a patient undergoing liver transplantation who sustained hemorrhage with the requirement for massive transfusion of coagulation factors via FFP, fibrinogen via cryoprecipitate and platelets. However, cryoprecipitate administration is not without risks as intraoperative cryoprecipitate administration during orthotopic liver transplantation has been associated with acute renal failure.[114]

The question remains whether blood product transfusion is a modifiable outcome in patients undergoing liver transplant or if it merely reflects the degree of challenge of each individual procedure due to patient- and surgery-specific variables. Ozier et al[98] evaluated the transfusion practice of 8 European centers in orthotopic liver transplantation and found modest use of blood products with median use of 5 units pRBCs, 6 units FFP, and 5 units of platelets but significant differences for pRBC and FFP transfusion between centers after adjustment for preoperative and intraoperative characteristics. The interprovider and intercenter variability described by some authors suggest blood product use may be somewhat modifiable to improve patient outcomes.[43,98]

Pharmacologic Interventions: Antifibrinolytics and Recombinant Factor VIIa

With improvement in transfusion requirements and thus a survival benefit, it is vital to consider interventions to further reduce clinical bleeding and the need for transfusion. Building from an understanding of the clinical coagulopathy associated with liver disease, particularly in the reperfusion stage of liver transplantation surgery, 4 pharmacologic agents have been suggested to be beneficial: ε-aminocaproic acid (EACA) (Amicar), tranexamic acid (TXA), aprotinin, and recombinant factor VIIa (rFVIIa). Aminocaproic acid and TXA are lysine derivatives that inhibit plasmin whereas aprotinin is a bovine-derived serine protease inhibitor that directly inhibits fibrinolysis.[3] rFVIIa serves to bind with transmembrane protein tissue factor and trigger the coagulation cascade in vivo.[3]

Restoration of hemostasis is often vital, but it is challenging to optimize the use of pharmacologic treatments aiming to reduce the need for blood product transfusion with the concomitant desire for increased graft survival. A very real, significant risk to administration of these medications is thrombosis. Hepatic artery and portal venous thrombosis can be catastrophic to perfusion of the newly transplanted liver, yet decreased blood pressure, anemia, and ischemia due to massive bleeding and requirement for massive transfusion similarly prevent adequate organ perfusion. Thus, antifibrinolytics and rFVIIa must be used thoughtfully in cirrhotic patients in certain clinical situations, such as with hyperfibrinolysis during liver transplantation or prior to invasive intracranial pressure monitoring in acute liver failure patients. Liver transplant anesthesiologists choose to use antifibrinolytic agents in situations of massive hemorrhage after transfusion of pRBCs and other blood components when there is concern that fibrinolysis is contributing to further bleeding. Liver transplant surgeons often describe this scenario intraoperatively when there had been some degree of hemostasis achieved in the surgical field, but once fibrinolysis occurs they note a generalized coagulopathy and bleeding or oozing from the tissue bed, not just from surgical incision and suture lines. Hyperfibrinolysis may be assessed with TEG or ROTEM (Figure 3). Clinically, treatment of hyperfibrinolysis is deemed successful by reduction in this generalized ooziness or bleeding, decreased drain output (once in the postoperative period), and resolution of the changes noted on TEG or ROTEM.

ε-Aminocaproic Acid

EACA, marketed as Amicar, inhibits plasmin, which is central to fibrinolysis and clot resolution. This phenomenon has been described since the earliest experimental liver transplant surgeries and at that time lead to a discussion of the risks (hypercoagulable state) and benefits (less bleeding) of treatment by EACA.[115,116] Kang et al[73] demonstrated evidence of fibrinolysis with whole blood clot lysis time < 120 minutes or clinical oozing in the surgical field when there had previously been clot. Their study spurred interest in the use of EACA in liver transplant patients as they were able to show both in vitro and in vivo normalization of fibrinolysis, with the administration of a single 1 g intravenous bolus of EACA. EACA is metabolized and eliminated by the kidney with 65% of the drug remaining unchanged in the urine. The half-life of EACA is 2 hours and it has been associated with renal complications such as acute tubular necrosis in patients undergoing cardiac surgery.[117]

Two additional studies examined the use of EACA. A single, retrospective study of a small, 13-patient subgroup analysis found no changes in transfusion as compared to a control group.[118] A larger prospective study, which included 132 patients randomized to EACA, TXA, or placebo, could not demonstrate a statistically significant difference in blood product use in the EACA group when compared to the control group, but did show an improvement in fibrinolysis and reduction in pRBC use intraoperatively in the TXA group.[119] However, nonequivalent dosing of EACA and TXA were used: the EACA group received 16 mg/kg/h and the TXA group received 10 mg/kg/h to maintain a ratio of 1.5:1, yet EACA is 6–10 times less potent than TXA.[119]

Tranexamic Acid

Similar to EACA, TXA is another lysine analog that prevents the conversion of plasminogen to plasmin, thereby inhibiting fibrinolysis.[120] TXA is more potent than EACA and has a longer half-life of 3 hours. TXA's antifibrinolytic activity is higher in peripheral sites such as kidney, GI tract, and prostate. TXA is excreted via the kidneys, again with 95% of

the drug eliminated unchanged in the urine.[117] In an in vitro model of hyperfibrinolysis, TXA has been shown to normalize coagulation parameters.[121] In vivo, 2 placebo-controlled, double-blind studies showed TXA to reduce blood product use compared to control. Boylan et al[122] studied 45 patients undergoing liver transplantation randomized 5:4 to TXA versus placebo and demonstrated a significant decrease in the perioperative exposure to donors of allogeneic pRBCs, FFP, cryoprecipitate, and platelets from a median of 43.5 to 20.5 units. This transfusion profile appears massive in modern terms, so the associated reduction in transfusion requirements may not necessarily be generalizable to liver transplantations that require fewer blood products. More recently, studies by Dalmau et al[119,123] demonstrated a small, but statistically significant difference in number of pRBC units transfused in patients receiving TXA versus EACA, but no differences in transfusion requirements, thromboembolic events, reoperation or mortality in patients administered TXA versus aprotinin. A third, smaller, randomized, controlled, and blinded study described favorable biochemical markers for reduced fibrinolysis, but not reduced transfusion requirement.[124] Molenaar et al[125] performed a systematic review of 23 studies that included 1407 patients and found that both aprotinin and TXA reduce transfusion versus placebo, but did not show an increased risk for hepatic artery thrombosis, venous thromboembolism, or perioperative mortality.

Aprotinin

Despite the withdrawal of aprotinin from use in the United States in 2007, aprotinin was reintroduced as an antifibrinolytic in Canada in late 2013 and the European Medicines Agency recommended its reintroduction in 2012.[126–128] Aprotinin is a bovine-derived serine protease inhibitor that directly inhibits fibrinolysis through fibrin inhibition.[3] Two prospective studies performed prior to the withdrawal of aprotinin appeared to show no difference in transfusion requirements when compared with patients given TXA.[123,129] This finding has been validated retrospectively by Massicotte et al[130] who did not detect a change in transfusion patterns between the last 300 patients given aprotinin and the next 100, who were given TXA, although the authors institution has a very restrictive transfusion profile with only 20% of liver transplant patients receiving an intraoperative pRBC transfusion.

Recombinant Factor VIIa

rFVIIa is strongly prothrombotic and acts via both tissue factor–dependent and tissue factor–independent pathways to activate factors X and IX, increasing thrombin generation at the site of vascular injury.[131] However, in vitro it does not improve induced hyperfibrinolysis.[121] There is a paucity of literature on its application during liver transplantation, which is currently an off-label indication.[132] Meijer et al[133] studied 6 patients given rFVIIa prospectively and found a sharp increase in thrombin generation after reperfusion when compared with historical controls. However, this timing corresponded with a shift in surgical practice from veno-veno bypass to caval preservation piggyback technique, clouding the interpretation of the findings of this study. One retrospective review showed benefit in administration of rFVIIa with reduction in pRBC transfusion by 3 units and FFP transfusion by 7.2 units in the group given rFVIIa, but only in patients with MELD score >20 and with a prolonged PT.[134] From a clinical perspective, once rFVIIa is administered, the PT shortens (often to the maximal degree detectable by the assay) and using the PT to indicate efficacy of response to rFVIIa or to trend changes in clinical coagulopathy is of limited utility.[135,136] Reduced levels and function of other coagulation factors, platelets, and fibrinogen may limit the effectiveness of rFVIIa.[137] Acidosis reduces the activity of rFVIIa by as much as 90% and the tissue factor-rFVIIa by as much as 60% with pH change from 7.4 to 7.0.[138] The half-life of administered rVIIa is reduced to 2 hours as compared to endogenous factor VIIa which is 4–6 hours; thus, there may be need for increased frequency of dosing in patients with liver disease and massive hemorrhage.

Two prospective, randomized, double-blind trials have investigated the use of rFVIIa during liver surgery. In 1 study, investigators administered placebo, 20 μg/kg of rFVIIa, or 80 μg/kg of rFVIIa to 204 noncirrhotic patients undergoing partial hepatectomy and found no significant decrease in the number of patients who required red blood cell transfusion.[139] In the other, 82 cirrhotic patients were given placebo or 20, 40, or 80 μg/kg of rFVIIa preoperatively prior to orthotopic liver transplantation.[140] No significant difference was found in the number of red blood cell transfusions required between the 4 groups. No significant adverse events were found with rFVIIa administration in either study.

Other Interventions

In addition to the therapies mentioned above to reduce the need for transfusion in the perioperative period, other practical measures exist to reduce transfusion requirements. When compared with historical controls, a dedicated liver transplant anesthesia service may reduce the average number of units of pRBCs transfused (15.2–5.2 units over a 5-year period; $P < .05$), reduce the average number of units of FFP transfused (28.9–3.4 units over a 5-year period; $P < .05$), and increase the proportion of patients extubated at the end of the case (from 0% to 56% over a 5-year period).[141]

Transfusion protocols may also help decrease the amount of blood products administered during liver transplant surgery. A small, randomized trial of 28 patients undergoing orthotopic liver transplantation demonstrated significant reduction in transfusion of FFP when using a transfusion protocol based on TEG results as compared with a transfusion protocol based on results of standard coagulation tests (mean 21.5 vs 12.8 units).[64] This work supports the earlier finding of Coakley et al[56] who, when comparing TEG, ROTEM, and conventional coagulation studies, found that treatment decision often varied depending on the assessment method used, particularly for FFP administration. Trzebicki et al[142] demonstrated a decreasing trend in transfusion of both FFP and pRBC with the use of ROTEM to guide transfusion therapy, although this trend did not reach statistical significance. ROTEM-guided transfusion protocols with reliance on coagulation factor concentrates, such as fibrinogen concentrate and 4-factor prothrombin

complex concentrate, have also been described as ways to decrease blood product transfusions without adverse consequences.[143]

Additionally, a newer form of FFP treated with solvent/detergent (S/D plasma) claims the benefits of pathogen inactivation, decreased numbers of cells and cell fragments, and a more standardized concentration of coagulation factors with the potential to cause fewer adverse effects compared with traditional FFP. One study comparing 2 groups of liver transplant patients randomized to receive either FFP or S/D plasma based on a TEG-guided transfusion protocol demonstrated fewer plasma transfusions in the S/D plasma group.[144] Unfortunately, increased hyperfibrinolysis has been correlated with S/D plasma administration, likely due to decreased α2-antiplasmin (an inhibitor of t-PA) in S/D plasma.[145] TXA may potentially counteract this increased hyperfibrinolysis when coadministered with S/D plasma.[146]

Another approach that may reduce pRBC transfusion rates focuses on a restrictive strategy to maintain low central venous pressure, which relies on fluid restriction, phlebotomy, liberal use of vasopressor medications, and avoidance of FFP transfusions.[95] Impressively, 79.6% of the 500 consecutive orthotopic liver transplants studied at this institution using this restrictive strategy received no blood products. Unfortunately, no control group was used in this study to compare the effect of such a restrictive strategy on postoperative kidney function or patient survival, although 1-month and 1-year survival rates were noted to be 94% and 86%, respectively, for these patients.[95]

Blood Scavenging Techniques

Blood loss scavenging techniques to salvage blood from the surgical field for autologous transfusion have been used during liver transplantation. In a retrospective case series, this has shown a variable impact on transfusion requirements. Hendriks[94] initially showed an increased transfusion requirement in patients in whom this technique was utilized, although this was not used uniformly and may reflect a selection bias. More recently, Sankarankutty et al[147] showed a decrease from 22.3 to 9.6 units of pRBCs after the introduction of this technique in a more systematic manner. Cell-saver use during living-donor liver transplant has been retrospectively shown to decrease allogeneic blood transfusion from 20 to 25 mL/kg in the group without cell-saver use to 5–10 mL/kg with cell-saver use.[148] Some controversy exists over the use of blood salvage and autologous blood transfusion during liver transplantation in recipients with hepatocellular carcinoma; however, current data suggest no increased risk of cancer recurrence.[149,150]

CONCLUSIONS

The coagulopathy of chronic liver disease is complex, owing to derangement of a variety of procoagulant and anticoagulant processes, which at early stages of the disease process may resemble a "normal" state. However, patients with end-stage liver disease are at increased risk of bleeding or clotting, potentially simultaneously. Both anticoagulant and procoagulant functions of the diseased liver are impaired such that assessment and management of bleeding and thrombosis are also simultaneously challenging. Furthermore, the coagulopathy of cirrhosis may be further altered during various stages of liver transplantation and by various medications and blood products administered. Surgical and anesthetic techniques have improved over the course of the past 20 years and there has been a striking reduction in the amount of blood transfused during liver transplantation. Additionally, the move away from traditional laboratory measures of coagulation such as PT and INR to newer functional viscoelastic measures of coagulation such as TEG and ROTEM shows promise for assessment of coagulopathy in patients with chronic liver disease presenting for surgery. Continued improvement in the understanding of the pathophysiology of liver disease with more reliance on early emphasis of treatment of coagulopathy with fibrinogen-containing products, and targeted treatment of coagulation failure with transfusion algorithms and pharmacologic methods to prevent fibrinolysis should lead to better prevention and management of the consequences of the complex coagulopathy present in cirrhosis.

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