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Coagulopathy in Cirrhotic Patients: Evaluation and Management

Richard Smith

Liver cirrhosis is a major source of morbidity and mortality worldwide. Liver cirrhosis is the 12th most common cause of death in the United States [49]. The incidence of cirrhosis continues to rise likely secondary to increasing rates of viral hepatitis and morbid obesity. From 2014 to 2015, cirrhosis deaths increased by 3.8% [69]. This trend has continued for the last decade and has resulted in increasing numbers of cirrhotic patients who will present for elective surgery and emergent surgery. Cirrhotic patients pose a challenge to surgeons based on liver dysfunction leading to increased complications and mortality. The two most common methods of determining risk in cirrhotic patients are the Child-Turcotte-Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scores [45, 77] (Table 24.1). A recent review of these scoring systems showed perioperative mortality of 2–10% for CTP A, 12–31% for CTP B, and 12–82% for CTP C patients with good correlation between CTP and MELD scores [41]. Both the CTP and MELD scores use the international normalized ratio (INR) to reflect the known hematologic derangements associated with liver dysfunction. Naturally there is a major concern for increased hemorrhage in the minds of surgeons operating on patients with cirrhosis.

There is a common misconception, though, within the surgical community that patients with chronic liver disease are "autoanticoagulated" [38]. The reality is that primary hemostasis and coagulation are preserved in most patients with cirrhosis [108]. To complicate matters further, the standard laboratory parameters (PT, aPTT, and INR) do not accurately reflect bleeding risk in cirrhotic patients. Portal hypertension appears to be the major risk factor for bleeding in cirrhotics. The relative balance between pro- and anticoagulation factors remains in cirrhotic patients, but the buffer (factors in quantities many times over physiologic need) is not present. Therefore, the increased risk for hemorrhage is seen in the most critically ill patients [29]. The reality is the hemostatic status of chronic liver disease is complicated. The hemostatic changes that occur in cirrhosis are a reflection of the interplay between decreases in both procoagulant and anticoagulant factors produced in the liver, increased production and decreased clearance of factors produced outside the liver, intravascular/systemic volume, and the clinical state of the patient [115]. This results in a somewhat tenuous but "rebalanced hemostasis" in most cirrhotic patients.

Rebalanced Hemostasis

Hemostasis can be broken down into three phases: primary, secondary, and tertiary. Primary hemostasis consists of platelet activation and formation of a platelet plug. Secondary hemostasis

R. Smith (✉)
Department of Surgery, University of Missouri, Columbia, MO, USA

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Table 24.1 Child-Turcotte-Pugh and MELD scores

	Points							
	1	2	3					
Encephalopathy	None	Grades 1–2 (acute)	Grades 3–4 (or chronic)	MELD =	$9.6 \times \log_e$	Serum	Creatinine	(mg/dL) +
Ascites	None	Mild to moderate (diuretic responsive)	Severe (refractory)		$3.8 \times \log_e$	Serum	Bilirubin	(mg/dL) +
Bilirubin (mg/dL)	<2	2–3	>3		$11.2 \times \log_e$	INR +	6.4	
Albumin (g/dL)	>3.5	2.8–3.5	<2.8					
INR	<1.7	1.7–2.3	>2.3					
Child-Turcotte-Pugh Class (add score for each parameter)								
Class A		5–6 points						
Class B		7–9 points						
Class C		10–15 points						

is activation of the coagulation cascade by tissue factor and platelet factors, resulting in thrombin activation and deposition of fibrin to stabilize the platelet plug. Tertiary hemostasis occurs with fibrinolysis of the clot mediated by tissue plasminogen activator and plasminogen [97]. Liver disease has complex effects on all three phases of hemostasis [51]. Bleeding time has been considered a measure of primary hemostasis. Bleeding time is prolonged in cirrhosis but does not appear to be of clinical significance [110]. Elevated bleeding time is not predictive of bleeding risk for liver biopsy or rate of bleeding from esophageal varices [6, 11]. Bleeding time has also been considered a measure of platelet function for their role in primary hemostasis.

The liver also has a direct role in platelet production via thrombopoietin, which stimulates megakaryocytes [60]. Platelets support hemostasis in two of the three phases of hemostasis. The first of these mechanisms is adhesion and forming aggregates adherent to damaged endothelial cells or to extracellular matrix structures exposed to flowing blood mediated by von Willebrand factor and fibrinogen [85]. The second is to provide suitable negatively charged phospholipid surfaces for formation of the enzymatic complexes needed for factor Xa and the formation of thrombin, which accelerates the formation of fibrin necessary to stabilize the clot [9].

A mild to moderate thrombocytopenia and a poorly defined change in platelet function are present in most patients with cirrhosis [78]. There is evidence in vitro that adhesion of platelets from patients with cirrhosis under flow conditions is normal, secondary to the increase of von Willebrand factor [58]. As shown previously, platelets support thrombin generation. The plasma of patients with cirrhosis shows a reduced endogenous thrombin potential when compared to controls. However, this can be corrected in the setting of thrombomodulin and normalization of the platelet count to 100,000/μl [101]. This suggests that platelet function in cirrhosis is intact and able to support adequate thrombin generation and that platelet numbers affect thrombin generation. This same study found, through analysis by linear regression, a rough estimate of the platelet numbers (56,000/μl) needed to support thrombin generation at the tenth percentile of the distribution of values recorded in the healthy control population [101]. This correlates well with the clinical data that showed an increase in bleeding complications for hepatitis C patients undergoing liver biopsy when the platelet count was <60,0000/μL [90]. However the standard practice of administering one adult equivalent unit of platelets prior to a procedure for patients with cirrhosis and thrombocytopenia has been shown to elevate platelet counts only marginally, with no or little effect on thrombin generation and thromboelastometry [104].

Sequestration of platelets from splenomegaly that develops in cirrhosis also complicates the interpretation of platelet function. A study of radiolabeled platelets in patients with splenomegaly demonstrated that up to 90% of radiolabeled PLTs underwent sequestration within minutes of transfusion. These radiolabeled PLTs redistributed to the peripheral circulation with injection of epinephrine [5]. It has been proposed that a similar redistribution of PLTs occurs after the endogenous release of epinephrine in response to bleeding in cirrhosis. In this situation, peripheral PLT counts would not represent the actual number of PLTs available at the time of a hemostatic challenge [117]. Response to platelet transfusions is also difficult to interpret when up to 90% of platelets transfused are rapidly sequestered [5].

The liver synthesizes the majority of coagulation factors (Fig. 24.1). As a result, all of the procoagulant factors decrease with the exception of factor VIII and von Willebrand factor (vWF) in cirrhosis. vWF appears to be increased through continuous low-grade activation of endothelial cells combined with decreased clearance by the liver. Factor VIII elevation may be due to compensatory production in other organs or increased level of the carrier protein vWF [115]. Levels of the endogenous anticoagulant factors, antithrombin, protein S, and protein C also decrease [59]. Levels of nitric oxide and prostacyclin increase. Levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI-1) reach a new equilibrium [115]. Tissue factor pathway

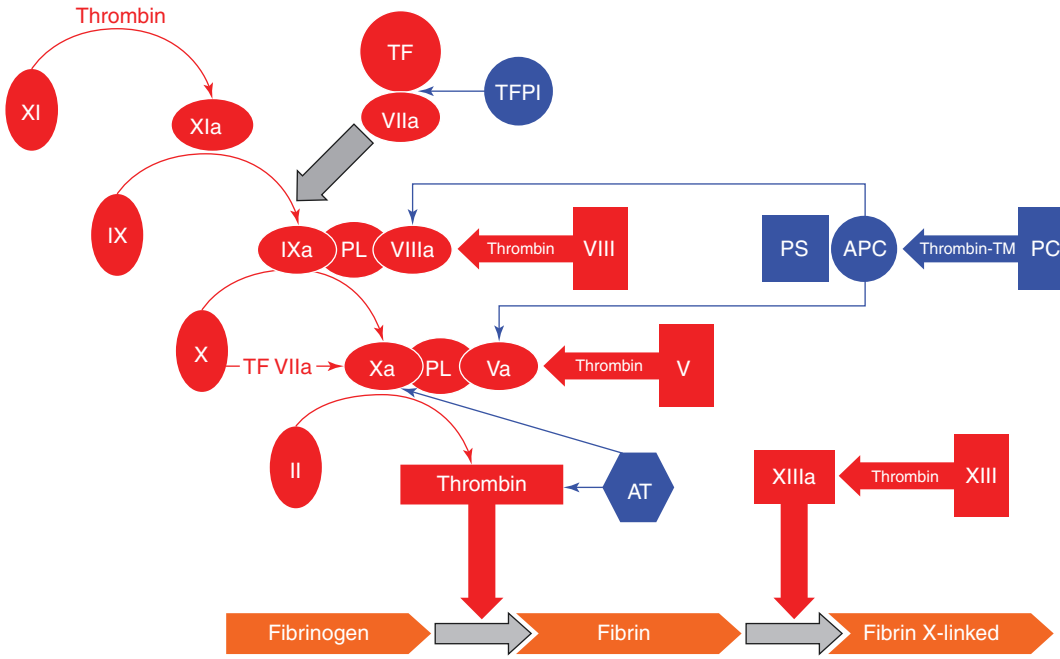

Fig. 24.1 Coagulation. Simplified representation of reactions leading to thrombin generation and inhibition. Roman numbers represent procoagulant (red) and anticoagulant factors (blue), respectively. APC activated protein C, AT antithrombin, PC protein C, PL negatively charged phospholipids on platelet membranes, PS protein S, TF tissue factor, TFPI tissue factor pathway inhibitor. (Reproduced from: Tripodi [106] with permission from Wolters Kluwer Health, Inc.)

inhibitor (TFPI) is synthesized by endothelial cells, and levels are normal or elevated in patients with chronic liver disease. TFPI downregulates the generation of thrombin. However, low levels of protein S, a cofactor, impair the TPFI anticoagulant pathway [76].

Similar to the clotting cascade, fibrinolysis (Fig. 24.2) appears to achieve a tenuous balance between pro- and antifibrinolytic pathways. In fibrinolysis under physiological conditions, plasminogen to plasmin conversion is regulated by profibrinolytic factors (tissue plasminogen activator [tPA], urokinase plasminogen activator, and activated factor XII). These effects are opposed by antifibrinolytic factors (tPA inhibitors [PAI-1], thrombin activatable fibrinolysis inhibitor [TAFI], and plasmin inhibitor. Derangements of this balance may result in hyperfibrinolysis or hypofibrinolysis [1]. Profibrinolytic changes in cirrhosis include increases in tissue plasminogen activator (tPA), plasmin activity, and a decrease in thrombin activatable fibrinolysis inhibitor (TAFI) and plasmin inhibitor. These changes are balanced by a decrease of plasminogen and an increase in plasminogen activator inhibitor (PAI-1) [24, 57] (Table 24.1). Some authors have described a hyperfibrinolytic state in cirrhosis [60]. Fibrinogen levels are often within the normal range in patients with stable cirrhosis, but decreased levels are found with advanced cirrhosis and in acute failure [17]. Dysfibrinogen or functionally aberrant fibrinogen has been shown in cirrhosis and is due to excessive sialic acid content [31]. Dysfibrinogenemia develops in 50–78% of patients with chronic liver disease. Regenerating hepatocytes synthesize an abnormal fibrinogen with increased sialic acid residues, which impairs polymerization of fibrin monomers [83, 106]. Based on the changes in both the pro- and antifibrinolytic actors, hyperfibrinolysis is likely to be overestimated. This overestimation is supported by a study that utilized thromboelastography (TEG) to show no evidence of fibrinolysis in 84 patients with

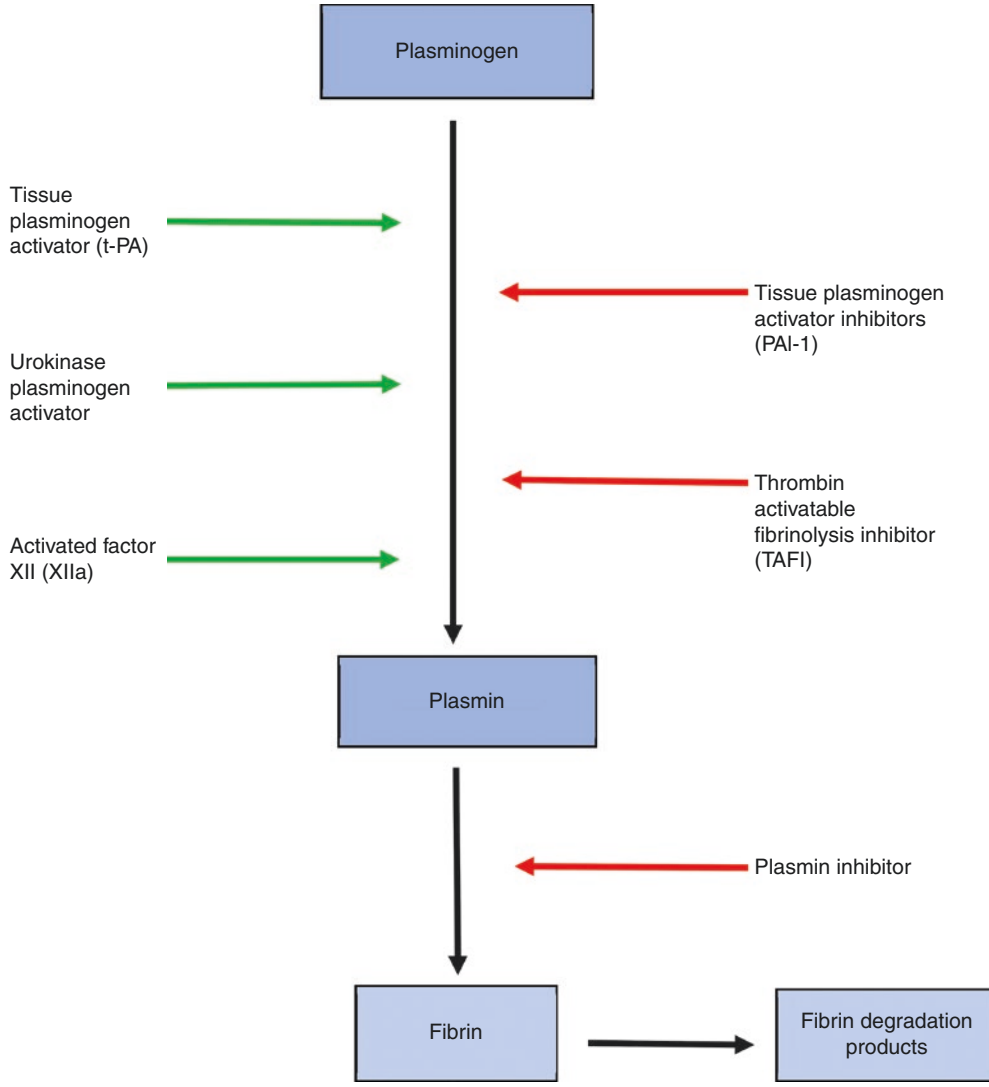

Fig. 24.2 Fibrinolysis

decompensated cirrhosis [72]. However, a true hyperfibrinolytic state may develop when a stressor overrides the fragile balance of pro- and antifibrinolytic factors present in patients with cirrhosis. Sepsis and release of endotoxin can set off a hyperfibrinolytic state through increased release of tPA [72].

Both procoagulant and anticoagulant drivers are lowered in cirrhosis, and compensatory mechanisms for hemostatic defects develop. Specifically, coagulation and fibrinolysis are in a rebalanced status because of a decline in both activators and inhibitors, and thrombocytopenia and platelet function dysfunction are compensated by elevated levels of VWF [115]. Despite the rebalancing of hemostatic factors, there are major alterations in the hemostatic pathways in most patients with liver disease. These include altered platelet and endothelial function, altered clotting factors, hyperfibrinolysis, dysfibrinogenemia, thrombocytopenia, and renal failure [17]. The elevated portal hypertension and splenomegaly, respectively, lead to alterations in hemodynamics and

increased platelet sequestration [115]. Despite a rebalanced hemostasis in patients with cirrhosis, this balance is less stable than in healthy patients because plasma levels of most factors are substantially reduced. This eliminates a natural buffer present in the healthy patient who has many times the necessary level for normal hemostasis (Fig. 24.3). This loss of buffer makes the hemostatic balance easily disturbed by complications of the disease including infections and renal failure leading to both bleeding and thrombotic events in these patients [60].

This "rebalanced hemostasis" of procoagulant and anticoagulant factors requires coagulation tests that can show the net result of these changes [21]. Basic labs (PT, aPTT, and platelets) fail to reflect the complex changes in the hemostatic profile of patients with liver disease. The platelet count does not take the elevated VWF levels or sequestration into account, and the PT and APTT are only sensitive for procoagulant factors and not the anticoagulant factors, tissue factor pathway inhibitor, or the role of the endothelium in hemostasis [60, 115].

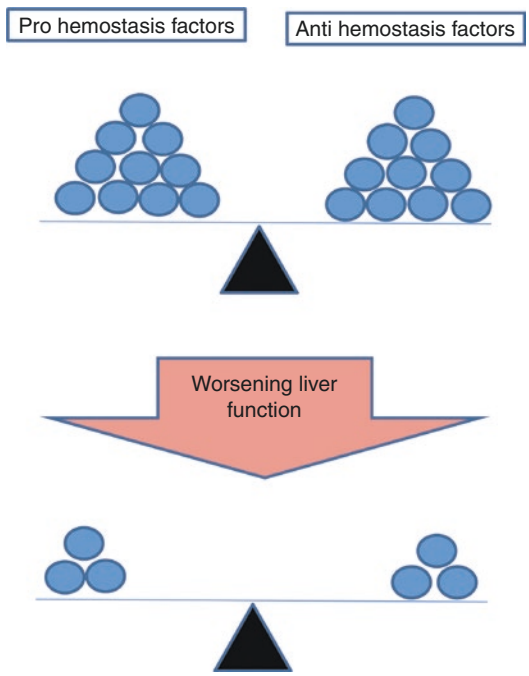

Fig. 24.3 Rebalanced hemostasis

Thrombin Generation Assay

A thrombin generation assay modified to include thrombomodulin is normal in patients with cirrhosis. Thrombomodulin is the main protein C activator operating in vivo but is not present in standard coagulation labs (PT, aPTT, INR) [100]. Therefore, patients with stable cirrhosis or patients undergoing liver transplantation (LT) can still generate thrombin at a normal to increased rate in the presence of a prolonged PT and APTT [59, 100].

Thromboelastometry/ Thromboelastography

Whole blood thromboelastography is another technique that may be helpful in the management of hemostasis in patients with liver disease [62, 98]. Whole blood viscoelastic tests evaluate the kinetics of coagulation, evaluating initial clot formation through final clot strength. As such they are a more comprehensive representation of the activity of procoagulants, natural anticoagulants, platelets, and the fibrinolytic pathway [83]. This overall assessment of hemostasis, including both plasmatic and cellular contributions, can be used to identify specific coagulopathies such as hyperfibrinolysis [88, 98]. There are two point-of-care devices (Thromboelastography (TEG), Haemonetics Corp., Braintree, MA, and Rotational Thromboelastometry (ROTEM), Tem International GmbH, Munich, Germany) available, and they have been routinely used to assess hemostasis and guide transfusion during liver transplantation [62, 88].

Five parameters are recorded in a standard TEG (Fig. 24.4). The reaction (R)-time (in minutes) represents the latency of clot formation from the beginning of the clotting reaction to the initial formation of fibrin and generally corresponds to the plasmatic component (INR and aPTT). The kinetic (K)-time (in minutes) describes the time required for the initial fibrin formation to reach a specific clot firmness. The alpha-angle (in degrees) reflects the rate of fibrin formation and cross-linking of platelets. The

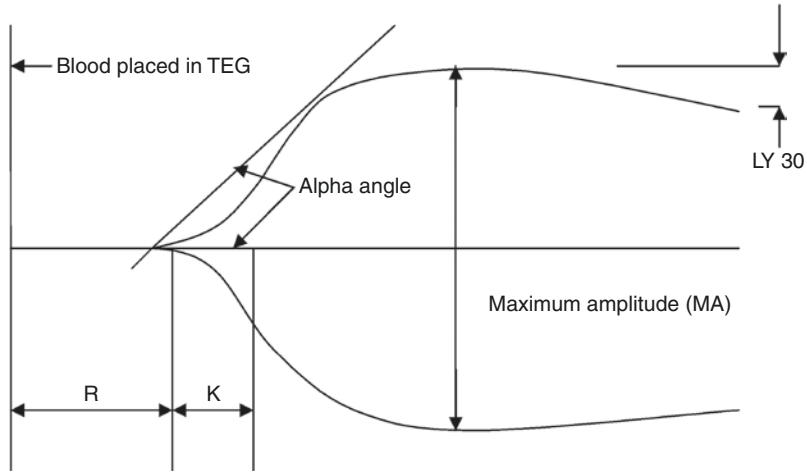

Fig. 24.4 Thromboelastography (TEG) tracing. (Reproduced from Chau et al. [20] with permission from BMJ Publishing Group Ltd.)

maximum amplitude (in mm) measures the maximum clot strength. The kinetic time, alpha-angle, and maximum amplitude are most dependent on platelet count/function and fibrinogen concentration. Finally, clot lysis at 30 minutes reflects clot dissolution and is a measure of fibrinolysis [98].

In stable cirrhosis, mean and median TEG parameters are generally within normal limits [98, 99]. However the maximum amplitude is decreased in proportion to the severity of thrombocytopenia. With greater degree of decompensation of cirrhosis (INR $\geq$1.5), the mean maximum amplitude of clot formation was below normal limits and correlated with a lower platelet count. The a-angle is also depressed in patients with decompensated cirrhosis and hypofibrinogenemia [98]. The findings from use of TEG in patients with cirrhosis support the observations made using thrombin generation assays, which showed that overall hemostasis is relatively well preserved [99, 100, 103, 107].

TEG has been shown to be superior to standard lab evaluation (INR, aPTT, or platelet count) for predicting esophageal varices rebleed rate. TEG parameters (r-time, k-time, and a-angle) on the day of variceal rebleeding showed significant differences when compared with the mean of the daily results in patients without rebleeding. In contrast, none of the standard laboratory tests of hemostasis differed between those who rebled and those who did not [19]. TEG-guided factor repletion has been shown to decrease red blood cell and plasma transfusion volumes [46, 61, 71, 88]. A small randomized trial that compared TEG versus standard lab testing (PT/INR) in patients undergoing orthotopic liver transplant (OLT) showed a significant decrease in FFP use in the TEG group compared to the standard lab test group but no differences in PRBCs administered and 3-year overall survival was seen between the two groups [113]. A follow-up study that used cutoffs 35% above baseline for transfusion of platelets and plasma did not result in increased bleeding or need for increased transfusion [114]. These studies suggest that TEG gives a more complete picture of the hemostatic picture in cirrhosis and the second study even suggests that the cirrhotic patient may even lean closer to thrombosis than bleeding. TEG monitoring during OLT to guide use of e-aminocaproic acid and aprotinin to treat hyperfibrinolysis has also been shown to decrease transfusion requirements [47, 75].

Infection and bleeding risk are tightly linked in cirrhosis. This is related to increased plasma concentrations of endothelium-derived endogenous heparinoids due to increased production and decreased hepatic clearance of these molecules [98]. TEG has also been useful in detecting infec-

tion in patients with cirrhosis. In a prospectively studied cohort of hospitalized decompensated cirrhotics, TEG parameters became more hypocoagulable in the patients who developed an infection compared to patients who did not develop an infection [72].

The appropriate "normal" range of TEG values in patients with cirrhosis has not been established. Some recent studies show a slower and less stable clot formation with a trend toward hypocoagulability [28, 53, 92]. Patients with cirrhosis may show a satisfactory coagulation balance without increased risk for bleeding, even if their TEG values are beyond the normal values for healthy patients [28]. The parameters for TEG correction during liver transplant have not been standardized, but authors have recommended two units of plasma for an R-time greater than 15 minutes, ten units of platelets for a maximum amplitude less than 40 mm, and six units of cryoprecipitate for an alpha-angle less than 40–45° [46, 75].

Unfortunately, to date, no studies have directly tested whether TEG, ROTEM, or other global tests such as thrombin generation testing are useful in predicting procedural bleeding risk in patients with liver disease [98]. In addition, the use of TEG- or ROTEM-guided transfusion in actively bleeding patients without liver disease was shown to reduce the amount of bleeding but has no clear effect on mortality [3]. The viscoelastic test values to trigger transfusion have not been validated, and large controlled clinical trials comparing different strategies and trigger values for transfusion of blood products are still needed [21].

Treatment Guidelines

Blood Products

The majority of clinical data for rebalanced hemostasis is the result of work done in OLT. It is common practice in some centers not to administer any blood products prior to or during the procedure unless active bleeding occurs [22, 42, 66, 79]. It would seem reasonable, and other authors have argued, to apply this to less complex procedures as well [115]. However, there are conflicting recommendations between societal guidelines. The American Association for the Study of Liver Diseases (AASLD) guidelines for liver biopsy carefully argue against prophylactic transfusion [84], whereas the Society of Interventional Radiology guidelines advise to correct an INR greater than 1.5 and a platelet count less than 50,000/μL [73].

Blood transfusion carries a number of significant risks. These include transfusion-related immunomodulation (TRIM); transfusion-associated circulatory overload; transfusion-associated acute lung injury (TRALI); hemolytic transfusion reactions; acute non-hemolytic transfusion reactions (febrile, allergic, or both in nature); transfusion-associated graft-versus-host disease; and transfusion-transmitted infection (bacterial, viral, and prion) [21]. The use of blood products during OLT has been shown to increase morbidity and mortality. Multiple studies have shown the intraoperative transfusion of red blood cells (RBCs) to be a major predictor of postoperative mortality [66, 80].

Because of the recognized risks of blood products, transfusion medicine has undergone a switch from product-specific to patient-specific care. Patient blood management (PBM) is defined as "the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome" [91]. The three pillars of PBM consist of treating preoperative anemia, reducing perioperative blood loss, and optimizing anemia tolerance [95]. More generally this describes identifying anemic patients preoperatively and intervening prior to surgery, using recognized techniques for minimizing blood loss, and using evidence-based patient-specific restrictive transfusion targets. This has been shown to decrease in-hospital mortality, length of stay, myocardial infarction/stroke, and infectious complications while decreasing overall transfusions of blood and factor products [52]. These concepts can be applied to patients with cirrhosis.

There is data to support a restrictive blood transfusion approach. A RCT of 921 patients with GI bleeding showed that a "restrictive" transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 7 g/dL and maintaining it at 7–9 g/dL) was associated with a significant decrease in mortality compared to a more traditional transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 9 g/dL and maintaining it at 9–11 g/dL). Patients with cirrhosis represented 31% of these patients and were shown to have a significantly lower early rebleeding and mortality rates with the restrictive strategy [109].

Given the limitations of current laboratory testing, the best strategy is to treat only those cirrhotic patients who develop significant hemostatic bleeding. Hemostatic bleeding is characterized by persistent oozing/bleeding at multiple sites and from nonidentifiable sources. Another marker is delayed bleeding after adequate control of surgical bleeding. When hemostatic bleeding occurs, then the platelet count, PT, APTT, and fibrinogen level may be useful in guiding the transfusion of blood products. More comprehensive measurements of hemostasis such as thromboelastography (TEG or ROTEM) may be useful to assess the hemostatic status intraoperatively [115].

There is no evidence for administering prophylactic FFP based upon INR [62]. AASLD in recognition of the limitations of conventional coagulation tests (PT and international normalized ratio [INR]) discourages the use of arbitrary values for the basis of the transfusion of plasma [84]. Intraoperative plasma transfusions are associated with adverse outcomes in liver transplantation [8, 66]. In addition, volume introduced through plasma transfusions may increase bleeding risks by raising portosystemic pressures [117]. Therefore, mild to moderate INR (<2.5) elevation should not be corrected with FFP before invasive procedures with the exception of intracranial pressure monitor insertion [50, 117]. One author recommends, if the INR is more than 2.5, to give 10 mg of intravenous (IV) vitamin K and check fibrinogen levels. Plasma is reserved for unresponsiveness to the vitamin K or in the presence of active bleeding [117].

Hypofibrinogenemia has been shown to increase blood product requirements. The use of fibrinogen concentrates for significant bleeding if accompanied by low fibrinogen is warranted. Fibrinogen concentrates have been shown to improve coagulation, reduce perioperative bleeding, and significantly reduce transfusion [21]. A fibrinogen concentration above 2 g/L has been shown to be the minimum concentration in vitro at which clot formation normalizes [12]. A concentration of <1.5–2 g/L or signs of functional fibrinogen deficit on TEG or ROTEM ROTEM/TEG should be triggered for fibrinogen replacement [50]. Fibrinogen concentrates should be used over cryoprecipitate when available to reduce the risk of pathogen transmission and immune-mediated complications [21].

Euthermia, free ionized calcium, and the acid-base balance all play a role in coagulation [115]. Plasma and RBCs contain citrate, which leads to hypocalcemia. Free ionized calcium should therefore be measured regularly and corrected to at least 1 mmol/L to prevent disorders of hemostasis [93].

Platelets

Currently there are no universally accepted clinical practice guidelines for platelet transfusion in patients with cirrhosis undergoing invasive procedures [2]. Despite the lack of high-quality evidence, the American Association for the Study of the Liver Diseases (AASLD) suggests prophylactic transfusion of PLTs for a PLT less than 50,000/mL [84, 117]. The recommendation from an institution with a large experience in treating patients with cirrhosis is that they be transfused platelets for counts less than 30,000/μL if undergoing a major procedure. A single dose (equivalent to single-donor apheresis PLTs or five-pooled whole blood-derived PLTs) of intraprocedural PLTs is given. They recognize that the peripheral count is unlikely to increase significantly or be maintained for a meaningful amount of time [117]. This recommendation is based on a retrospective study evaluating thrombocytopenic patients with hematologic malignancies undergoing transjugular liver biopsy. There were no

bleeding complications in the entire cohort despite half the patients couldn't reach the goal of greater than 30,000/mL with multiple transfusions prior to the procedure [112].

Eltrombopag is an oral thrombopoietin-receptor agonist approved for use in patients with chronic immune thrombocytopenia. Eltrombopag was shown to increase platelet counts in patients with thrombocytopenia and hepatitis C [67]. This study was a placebo randomized control trial to assess ability to get patients onto retroviral therapy and was successful. A larger study was performed to examine if the drug could decrease the use of platelets for patients undergoing invasive procedures. This RCT did indeed show a significant increase in platelet counts and a decreased need for transfusion of platelets but an increased risk of mesenteric thrombosis. This result led the authors of the study to recommend against its use perioperatively until further studies can be done [2].

Preoperative Optimization

Iron deficiency anemia is often seen in cirrhosis [33]. The use of iron has been found beneficial in patients with iron deficiency anemia and is a correctible problem in cirrhotic patients preoperatively [26, 86]. Erythropoietin is produced in the kidney, stimulating erythrogenesis. Erythropoiesis begins within 3 d of administartion, and the equivalent of one unit of blood is produced in 7 d and five units within 28 d. This can be associated with functional iron deficiency, and iron supplementation is recommended for patients undergoing rEPO therapy [26, 106]. One center used rEPO 20,000 U subcutaneously twice a week or 40,000 U once a week preoperatively until the hematocrit reached 45% in Jehovah's Witness patients awaiting OLT.

Hemostatic balance in cirrhosis may be variable depending on the degree of liver dysfunction, underlying cause of liver disease, and current clinical state. The existence of *bacterial infection* has been shown to increase the risk of bleeding, mortality, and failure to control bleeding in patients with variceal bleeding [13, 35, 111]. Prophylactic administration of antibiotics to patients with cirrhosis is known to reduce mortality and improve hemostatic function in the setting of variceal bleed. The exact mechanism for this is unknown. Patients at risk for bacterial infections should receive prophylactic antibiotics to optimize hemostatic function. The adequate treatment of any infections before invasive procedures is also paramount [115, 117].

Renal insufficiency is associated with an increased risk of bleeding [43, 74]. The effects of kidney failure on hemostasis are complex and include the effect of uremia on platelet function [70]. The uremic effect on platelets is due to decreased platelet aggregation and adhesion. Dialysis can improve platelet function by removing uremic toxins and decrease risks of bleeding associated with volume overload [21, 117].

Fibrinogen levels can be decreased in cirrhotics. Patients undergoing OLT with low preoperative plasma fibrinogen ($\leq$2 g/L) have significantly higher rates of transfusion of RBCs than in the patients with fibrinogen values >2 g/L [25]. However, although preemptive administration of fibrinogen concentrate can increase plasma levels of fibrinogen to normal values and increase maximum clot firmness on TEG, it does not reduce the need for RBC transfusions in LT [87].

Control Portal Pressures

Portal hypertension is the main consequence of cirrhosis and is responsible for the majority of its complications. As such, it is the major cause of the increased risk of bleeding associated with cirrhosis. Portal pressure can be directly measured as the hepatic venous pressure gradient (HVPG). The HVPG has been shown to be more accurate than liver biopsy in predicting development of complications of cirrhosis [10]. Portal hypertension can be divided into mild PH (HVPG >5 but <10 mm Hg) and those with clinically significant portal hypertension (HVPG >10 mm Hg) [32]. Clinically significant PH is associated with an increased risk of varices, variceal hemorrhage ascites, encephalopathy,

postsurgical decompensation, and hepatocellular carcinoma (HCC) [16, 36, 81, 82].

Patients with cirrhosis and portal hypertension have a response to volume loading that can exacerbate bleeding. Volume loading leads to increased blood pooling in the splanchnic circulation, by a greater magnitude than in the central and arterial circulation [21]. The resultant increase in portal venous pressure from volume loading can lead to increased bleeding. Intraoperatively, an important strategy to prevent bleeding during invasive procedures is to maintain a low splanchnic and portal pressure. This is primarily achieved by using CVP as a surrogate for portal pressures and maintaining a low total circulating volume intraoperatively [94]. A variety of methods are used to maintain a low CVP including a restrictive infusion policy, forced diuresis, and preoperative phlebotomy [39, 64, 65, 115]. Maintaining a low CVP has been shown to considerably reduce perioperative blood loss during liver resection and liver transplant surgery [44, 94]. A major concern with the low CVP approach is to maintain sufficient tissue perfusion, especially of the kidneys. This can be accomplished through the use of vasoconstrictors [65]. In a randomized controlled trial by Feng et al., comparing the use of low and normal CVP during liver transplantation, a significant reduction of blood loss was achieved with no adverse effect on kidney function [30].

Antifibrinolytic Therapy

Antifibrinolytic therapy has been shown to decrease blood loss and need for transfusion [40]. Aprotinin has been shown to reduce blood loss and transfusion requirements [37]. Aprotinin is a bovine-derived serine protease inhibitor that leads indirectly to diminution of fibrinolysis [17]. However, it was withdrawn from the market due to safety concerns [50]. Antifibrinolytic agents, such as aminocaproic acid (EACA) and tranexamic acid (TA), are derivatives of lysine that inhibit plasmin. Lysine analogues, such as tranexamic acid, have been shown to have a lower risk of death when compared to aprotinin. Meta-analyses have shown both tranexamic acid and aprotinin to reduce RBC transfusion during OLT [68]. Tranexamic acid competitively inhibits the activation of plasminogen to plasmin. The usual dose of tranexamic acid is in 1–2 g increments. TEG/ROTEM can be used to guide further doses [21].

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) is a hemostatic agent approved for hemophilia. rFVIIa offers the theoretical advantage of augmentation of the physiological thrombin accumulation at the site of injury, enhanced activation of platelets, and avoids excessive volume [17]. rFVIIa binds to the surface of activated platelets and to tissue factor (TF) at sites of vascular injury activating factor X. Factor X augments the conversion of prothrombin to thrombin forming the hemostatic plug (Fig. 24.1). Unfortunately, randomized trials assessing the use of rFVIIa in upper GI and variceal bleeding failed to show improvement in blood use or mortality [14, 15]. The TF-independent clotting potential of rFVIIa has raised concern for unintended, off-target thrombosis [34]. Meta-analysis and systematic reviews of the use of rFVIIa in hepatic surgery (including transplantation) have failed to show a benefit in the number of blood transfusions yet showed, but they did show a significant increase in arterial thrombotic complications [20, 55, 116]. Despite these findings, based on its mechanism of action, it may still have a role as a rescue agent in severe hemorrhage when conventional blood component replacement is insufficient and the thromboembolic risk is outweighed by the risk of ongoing bleeding [17, 34, 54].

Desmopressin

Desmopressin (DDAVP, 1-deamino-8- D-arginine vasopressin) is an analogue of the antidiuretic hormone vasopressin, which increases endogenous secretion of vWF and FVIII. Surprisingly, in light of the already elevated levels of vWF and factor VIII in cirrhosis, the agent shortens bleeding time in cirrhotics. However, clinical trials in cirrhosis have been disappointing [17].

Prothrombin Complex Concentrate

Factor concentrates like a prothrombin complex concentrate (PCC) are pharmaceutical agents in lyophilized volume. As such they are highly concentrated, low volume, virally inactivated products that do not require thawing and can be rapidly administered [7]. The nonactivated vitamin K-dependent coagulation factors in PCC are 25 times more concentrated when compared with FFP [18]. The use of PCC may mitigate infectious risk, decrease volume, and decrease administration time associated with FFP [23]. The concern with these agents is their effectiveness and the risk for thromboembolic complications. Retrospective studies have been inconclusive in the decrease in blood product usage in the setting of liver transplant and limited in evaluation for thrombotic complications [23, 48]. A randomized controlled trial (the PROTON trial) studying prothrombin complex concentrate (PCCs) effect on RBC transfusion requirements in OLT is currently in progress [4].

Cryoprecipitate

There is no consensus regarding appropriate levels of fibrinogen necessary in nonbleeding or bleeding cirrhotic patients [117]. Hematologic defects have been seen in studies looking at massive hemorrhage when fibrinogen levels have decreased below 100 mg/dL [56]. Based on these studies that did not specifically look at cirrhotics, a fibrinogen level of 100 mg/dL as a minimum has been recommended for perioperative bleeding [63, 96]. Cryoprecipitate, which has a higher concentration of fibrinogen, should be used instead of FFP for replacement. This avoids the increased volume issues [117].

Conclusions

Under general conditions the patient with liver cirrhosis is in hemostatic balance and at risk for both bleeding and thrombotic events. Standard laboratory evaluations (platelet count, PT, and APTT) are poor predictors of bleeding risk. Furthermore, attempts to prophylactically correct abnormal values with platelet concentrates or plasma do not reduce bleeding. The use of blood products to correct abnormalities may actually exacerbate bleeding by increasing volume load. Treatment of coagulopathy should only be treated when experiencing active bleeding of hemostatic origin.

The strategy for preventing bleeding should be keeping CVP and total circulating volume low intraoperatively. Modifiable risk factors for bleeding in patients with cirrhosis such as infection and renal failure should be addressed preoperatively. Ideally procedures should be undertaken in facilities with experience in dealing with patients with cirrhosis such as transplant centers where physicians from all disciplines dealing with liver disease can provide a comprehensive treatment plan. The concept of rebalanced hemostasis in patients with liver disease and the above strategies have been implemented successfully in liver transplantation. Although it is clear that prophylactic correction of abnormal hemostatic parameters should be abandoned, specific data to support treatment schemes based on this new approach are scarce. Patients with cirrhosis are a heterogenous group and can present in a variety of clinical situations. Although these patients are better off as a group when treated as outlined, it is possible that a true coagulopathy does exist in an individual patient. Because of the lack of a clinically applicable coagulation test that reliably predicts the risk of bleeding, clinicians currently cannot identify individual patients with an increased bleeding risk, apart from the risk factors mentioned in this chapter. Further research is needed to accurately predict bleeding risk in patients with liver disease.

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