Concise Definitive Review

Jonathan E. Sevransky, MD, Series Editor

Treatment of Coagulopathy Related to Hepatic Insufficiency

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Objectives: To provide a concise review of the medical management of coagulopathy related to hepatic insufficiency. This review will focus on prevention and management of bleeding episodes in patients with hepatic insufficiency. The treatment and prevention of thromboembolic complications will also be addressed.

Data Sources: Electronic search of PubMed database using relevant search terms, including hepatic coagulopathy, hemorrhage, liver diseases, blood coagulation disorders, blood transfusion, disseminated intravascular coagulation, and liver failure. Subsequent searches were done on specific issues.

Study Selection: Articles considered include original articles, review articles, guidelines, consensus statements, and conference proceedings.

Data Extraction: A detailed review of scientific, peer-reviewed data was performed. Relevant publications were included and summarized.

Data Synthesis: Available evidence is used to describe and summarize currently available tests of hemostasis, utilization of prohemostatic agents, transfusion strategies, use of prophylactic anticoagulation and treatment of thromboembolic events in patients with hepatic insufficiency.

Conclusions: Dynamic changes to hemostasis occur in patients with hepatic insufficiency. Routine laboratory tests of hemostasis are unable to reflect these changes and should not be used exclusively to evaluate coagulopathy. Newer testing methods are available to provide data on the entire spectrum of clotting but are not validated in acute bleeding. Prohemostatic agents utilized to prevent bleeding should only be considered when the risk of bleeding outweighs the risk of thrombotic complications. Restrictive transfusion strategies may avoid exacerbation of acute bleeding. Prophylaxis against and treatment of thromboembolic events are necessary and should consider patient specific factors. (*Crit Care Med* 2016; 44:1927–1933)

Key Words: blood coagulation factors; coagulopathy; hepatic insufficiency; liver failure; prothrombin complex concentrate

Management of hepatic coagulopathy has traditionally been addressed dogmatically, but new methods to evaluate the risk of bleeding and new strategies to address acute bleeding episodes are challenging the status quo. It is now recognized that hepatic insufficiency results in a myriad of profound changes in the hemostatic system. Concomitant reductions in both pro- and anticoagulant factors create a dynamic rebalancing of hemostasis, but the balance can be easily disrupted (1–3). Routine tests of hemostasis, such as activated partial thromboplastin time (aPTT) and prothrombin time/international normalized ratio (PT/INR), are unable to fully characterize this rebalanced coagulopathy. Using the normalization of aPTT and PT/INR as an endpoint of prophylactic and resuscitative strategies should be avoided. Advances in transfusion protocols, notably with lower transfusion triggers, have been shown to reduce rebleeding risk and transfusion-associated complications. Thrombotic complications are also commonly seen in patients with hepatic coagulopathy. Prophylaxis against and treatment of these complications are necessary (4).

PATHOPHYSIOLOGY

Changes in all phases of hemostasis are seen in liver disease (**Table 1**). Due to the liver's role in the synthesis of most coagulation factors, reductions in procoagulant and anticoagulant factors, fibrinolytic factors, and antifibrinolytic proteins are seen (5).

Production of all procoagulant factors, with the exception of factor VIII, occurs in the liver. Consequently, levels of procoagulant factors, including prothrombin, V, VII, IX, and X, are reduced in hepatic insufficiency (6). Production of anticoagulant factors, including antithrombin, protein C, and protein S, are also decreased (6). Factor VIII levels are frequently elevated in liver failure, possibly due to extrahepatic synthesis, up-regulation of alternate production pathways, or reduced clearance (7).

Thrombocytopenia is common in both acute and chronic liver disease, and it has multiple underlying etiologies. Liver

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Dr. Barton disclosed off-label product use (the use of recombinant factor VIIa, prothrombin complex concentrates, desmopressin, eltrombopag, and tranexamic acid are all off-label uses for indications discussed in this article).

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TABLE 1. Changes to Hemostasis Seen With Hepatic Insufficiency

Change to Hemostatic System	Proteins Affected	Pathophysiology of Change
Decreases in procoagulant proteins	↓ Prothrombin ↓ Factor V ↓ Factor VII ↓ Factor IX ↓ Factor X	Decreased hepatic production
Decreases in anticoagulant proteins	↓ Antithrombin ↓ Protein C ↓ Protein S	Decreased hepatic production
Increases in procoagulant protein	↑ Factor VIII	Extra-hepatic synthesis Up-regulation of alternate production pathways Reduced clearance
Thrombocytopenia, functional platelet defects	↓ Platelets	Decreased thrombopoietin production Increased platelet consumption Congestive splenomegaly in cirrhosis pooling platelets in spleen
Increases in platelet adhesive protein	↑ von Willebrand factor	Increased production Reduced hepatic clearance
Changes in fibrinogen	↔ Fibrinogen	Increased fibrinolysis in acute liver failure Hyperfibrinolysis in advanced liver disease Often normal in stable chronic disease

failure results in decreased thrombopoietin production, which, in turn, leads to decreased platelet production (8). Increased platelet consumption, possibly from chronic, low level disseminated intravascular coagulation (DIC), may also be a contributing factor (9). Thrombocytopenia can be further potentiated by continued alcohol use and its toxic effects on the bone marrow, folic acid deficiency, or myelosuppression from hepatitis viruses (10, 11). In patients with cirrhosis, portal hypertension can cause congestive splenomegaly, which results in pooling of platelets in the spleen (12). Further complicating this picture are the platelet function defects found in liver disease patients. Defects are seen in both platelet aggregation and platelet vessel wall interaction necessary for primary hemostasis (5, 13).

The thrombocytopenia of liver disease is balanced by the concomitant, substantial increase in the concentration of platelet adhesive protein von Willebrand factor (VWF), which is produced by endothelial cells and megakaryocytes (7, 14). High plasma levels of VWF likely result from increased production, reduced hepatic clearance, and increased endothelial activation seen in portal hypertension and bacterial infection (15–17). Although it has been shown that the VWF in liver patients has reduced functionality, the elevated levels are still able to partially compensate for platelet defects and contribute to primary hemostasis (15).

Fibrinogen levels are often decreased in acute liver failure and advanced disease, but frequently remain normal in chronic stable disease (18). The fibrinolytic system is under the strict control of activators, including tissue plasminogen activator (tPA) and urokinase plasminogen activator, and inhibitors of tPA and thrombin activatable fibrinolysis inhibitor. In liver disease, reductions in both the activators and inhibitors of the fibrinolytic system are seen (5, 18–20). Overall, while still debated, it appears that a state of hyperfibrinolysis predominates in patients with active bleeding.

The coagulopathy associated with acute and chronic liver failure differ significantly. Changes to liver structure in chronic liver failure lead to portal hypertension, hypersplenism, thrombocytopenia, and gastroesophageal varices, each of which is associated with increased bleeding risk. Acute liver failure is not associated with significant portal hypertension, and the thrombocytopenia seen is typically modest. Therefore less significant bleeding after an invasive procedure is expected as compared to bleeding in chronic disease states (21, 22).

Concomitant disease states alter the hemostatic balance in liver failure. Bacterial infections in these patients are linked to an increased risk of and an inability to control bleeding, most prominently acute variceal bleeding (23–25). While the exact mechanism of infection inducing or potentiating bleeding is still debated, endotoxins and cytokines are implicated (25). Endotoxins and cytokines produced in the presence of bacterial infection can induce DIC, inhibit platelet function, and enhance the effects of nitric oxide (25, 26). Adequate treatment of known infection and prophylaxis against potential infection is required (27). Renal insufficiency is also a common complication of liver dysfunction, leading to increased risk of bleeding through acquired uremic platelet dysfunction and impaired platelet vessel wall interactions (28).

CURRENT COAGULATION TESTING METHODS

Laboratory values are routinely used to assess bleeding and thrombotic risk in patients with hepatic insufficiency. Unfortunately, currently available laboratory tests are unable to provide a comprehensive view of hemostatic changes in these patients (**Table 2**).

Basic laboratory coagulation tests, including PT/INR and aPTT, are frequently used in patients with hepatic coagulopathy. Although PT, INR, and aPTT were created to monitor vitamin K antagonist therapy and screen for congenital coagulopathies,

TABLE 2. Advantages and Limitations of Available Laboratory Measurements in Patients With Hepatic Insufficiency

Laboratory Test	Advantages	Limitations
Prothrombin time/international normalized ratio	Widely available	Elevations do not correlate to bleed risk
Activated partial thromboplastin time	Widely available	Limited clinical relevance
Platelet count	Very low levels correlate to bleed risk Widely available	Does not provide information on platelet function Does not account for elevated von Willebrand factor
Bleeding time/platelet function assay	Assesses platelet function	Results do not correlate to bleed risk Limited availability
Thromboelastography	Assesses all stages of hemostasis Can identify hyper- and hypocoagulability Increasingly available Can guide transfusion therapy	Requires experience to interpret results Parameters not standardized

the tests have been widely applied. The dynamic effects to the hemostatic system seen in hepatic coagulopathy are unable to be fully represented by these tests (14, 29). PT/INR and aPTT testing should be interpreted with caution, knowing that the full spectrum of changes seen in hepatic coagulopathy cannot be represented by their result.

Thrombin generation testing is a more comprehensive method of evaluating hemostatic capacity in liver disease. This test measures the amount of thrombin generated during in vitro coagulation. As compared to traditional tests that are elevated in liver disease, thrombin generation is often not affected, and may be enhanced (30). It remains unclear if thrombin generation testing can predict either bleeding or thrombosis, and, for now, routine use cannot be recommended.

Whole blood coagulation tests, such as thromboelastography or rotational thromboelastometry, provide data on the entire spectrum of clotting. These tests deliver information on phases of coagulation over time, including initial platelet adhesion, clot formation, clot stability, and fibrinolysis. These tests can inform providers of the presence of hypercoagulability and hypocoagulability. This more specific data can direct the clinician to which pathways of coagulation are affected, and therefore allow treatment directed at the identified derangements (14, 31, 32). These tests have been routinely used to guide transfusion requirements during liver transplantation and to guide resuscitation in patients without liver disease (14, 31). Important hindrances to widespread application include nonstandardized hemostasis evaluation parameters and, while access is expanding, availability of the technology. At this time, thromboelastography is not validated to predict bleeding or thrombosis in patients with hepatic coagulopathy not undergoing liver transplantation, but it presents a promising option to validate or refute results of more standard hemostatic tests.

TREATMENT

Despite an increased awareness of the pathologic changes contributing to hepatic coagulopathy, management of acute bleeding episodes often remains largely unchanged. There are no guidelines available to direct the management of blood product transfusion, fresh frozen plasma (FFP), or coagulation factor concentrates such as recombinant factor VIIa (rfVIIa) or prothrombin complex concentrates (PCCs). Goals of resuscitation should focus on problem-based resuscitation and management, rather than correction of routine laboratory values. This practice is supported by liver transplantation data, where many patients are able to undergo transplant with minimal blood product administration despite abnormal laboratory values (33, 34).

PROPHYLACTIC STRATEGIES PRIOR TO INVASIVE PROCEDURE

The routine practice of empiric blood product transfusion prior to invasive procedures should be avoided. There is a lack of evidence supporting empiric transfusion not targeting transfusion thresholds, likely because this practice is targeted at normalization of routine laboratory parameters rather than bleeding diatheses. **Table 3** summarizes the advantages and limitations of commonly available transfusion products and hemostatic agents.

Routine transfusion of FFP has not been shown to be efficacious for prophylaxis of bleeding, and is not recommended as patients are unlikely to benefit (35). Response to FFP is unpredictable and often does not fully normalize INR or PT in this population. Patients undergoing a very high risk procedure where the benefit of decreasing bleeding outweighs transfusion risk, such as intracranial pressure (ICP) monitor placement, are potential candidates for FFP transfusion.

Recent data supports a reasonable platelet transfusion threshold of 50,000/μL prior to high risk procedures (36–38). In the case of major neurologic procedures, this recommendation increases to greater than 100,000/μL. At this threshold, sufficient thrombin production is seen and elevations in VWF likely balance the relative thrombocytopenia. Given the risk of transfusion reaction and other potential side effects, administration should be reserved for patients falling below these thresholds.

TABLE 3. Advantages and Limitations of Available Transfusion Therapies and Prohemostatic Agents in Patients With Hepatic Insufficiency

Product	Advantages	Limitations	Suggested Transfusion Trigger
Packed RBCs	Maintains tissue perfusion and prevents hemorrhagic shock in acute blood loss anemia	Transfusion-associated adverse events Over-transfusion impairs hemostasis via physical pressure increases or induced coagulopathy	Hemoglobin 7 g/dL
Fresh frozen plasma	Replaces hemostatic proteins	Transfusion-associated adverse events Large volume transfusion impairs hemostasis via exacerbation of portal hypertension	None available
Platelets	Improves primary hemostasis via increasing thrombin production	Transfusion-associated adverse events	50,000/μL
Recombinant factor VIIa	Small volume Timely normalization of standard hemostatic tests	Cost Thrombosis Promotes targeting of standard hemostatic test normalization Lack of proven efficacy in active bleeding	Risk of bleeding outweighs risk of thrombotic complications
Prothrombin complex concentrates	Small volume Balanced resuscitation of pro- and anticoagulant factors	Cost Thrombosis Lack of proven efficacy in active bleeding	Risk of bleeding outweighs risk of thrombotic complications
Tranexamic acid	Small volume	Lack of proven efficacy in active bleeding	Risk of bleeding outweighs risk of thrombotic complications
Cryoprecipitate	Small volume Replaces fibrinogen	Only replaces fibrinogen, factor VIII and von Willebrand factor	Fibrinogen < 150 mg/dL

Medications utilized to improve platelet count and function have been investigated without clear benefit. Eltrombopag, a thrombopoietin receptor agonist, has been shown to increase thrombotic complications and should not be routinely used (39). Desmopressin, a synthetic analogue of human antidiuretic hormone, has been studied to support hemostasis in patients with chronic liver disease with mixed results (40–45). The available clinical data for desmopressin use in disparate mechanisms of bleeding, from dental extraction to variceal bleeding, has shown little impact on blood loss. The role of desmopressin in hemostasis remains unclear, and routine prophylactic use is not recommended for hepatic coagulopathy.

Case reports and series suggest rFVIIa for INR normalization and reduction of bleeding risk prior to high risk surgical procedures, namely ICP monitor placement and liver biopsy, may be effective (46–53). This practice is often favored over FFP administration due to more consistent and timely INR normalization and lower volume requirements (48). Available literature utilizes a dose of 20–40 μg/kg administered 30 minutes prior to procedure. Limitations to rFVIIa use in this setting include cost, targeting PT and INR normalization despite these tests being inadequate assessment of coagulation, and thrombosis (54, 55).

Coagulation factor concentrates, such as PCCs, offer potential advantages over rFVIIa in reduced thromboembolic complications, and over FFP via reduced volume requirements. While studies reveal reductions in blood loss during liver transplantation, use outside of this population cannot be recommended routinely due to lack of supporting evidence (2, 56).

The contribution of vitamin K deficiency to the coagulopathy of liver disease is controversial. Empiric IV vitamin K administration should be considered in all patients, as treatment of known or suspected deficiency is associated with few adverse events. Dosing of 10 mg daily for 2–3 doses should provide sufficient replacement.

TREATMENT STRATEGIES DURING ACTIVE BLEEDING EPISODES

There are no guidelines for the resuscitation of actively bleeding patients with hepatic insufficiency. An increasing body of evidence supports more restrictive transfusion strategies in patients with hepatic insufficiency than are frequently utilized. Transfusion of packed RBCs, FFP, and platelets have been associated with increased morbidity and mortality in patients with hepatic insufficiency (57–59). Transfusion increases circulating blood volume, resulting in the reversal of splanchnic vasoconstriction induced by hypovolemia. This decrease in splanchnic vasoconstriction allows for increasing blood flow and pressure which impairs clot formation. In patients with portal hypertension, an increase in circulating volume from resuscitation aimed at completely replacing blood loss can prompt rebound escalations in portal pressure. This increased portal pressure can lead to increased bleeding. More restrictive resuscitative strategies in patients with hepatic insufficiency lead to reduced volumes transfused, allowing for hemodynamic stabilization and increased survival (60, 61). Transfusion-induced coagulation abnormalities are also of concern.

The use of a restrictive blood transfusion strategy with a hemoglobin threshold for transfusion of 7 g/dL and a target post transfusion hemoglobin level of 7–9 g/dL has been shown to increase survival and reduce the risk of further bleeding and complications in patients with upper gastrointestinal bleeding events (61). Application of this restrictive transfusion strategy to massive bleeding episodes is not supported by the available literature at this time, likely due to the inability to precisely target values in these situations.

Maintaining platelet counts above 50,000/μL is suggested (36–38). In the setting of intracranial hemorrhage, it is recommended that platelet counts are maintained above 100,000/μL. Targeting fibrinogen levels above 150 mg/dL has been suggested, but this threshold has not been thoroughly tested (62).

Efforts to correct coagulopathy via transfusion of FFP are fraught with disadvantages. Large volumes are required, typically 20–40 mL/kg, to fully replenish coagulation factors. As mentioned previously, this large volume transfusion can impair primary hemostasis and increase the risk of rebleeding. Even with full treatment doses, standard laboratory parameters are rarely normalized. Adverse events associated with FFP use include transfusion-related acute lung injury, transfusion-associated cardiac overload, pulmonary edema, and anasarca.

Potential prohemostatic strategies requiring less volume while correcting coagulopathy include the use rFVIIa, PCCs, and antifibrinolytic agents, such as tranexamic acid.

The role of rFVIIa in active bleeding remains limited. Initial data suggested decreased transfusion requirements during liver transplantation with prophylactic rFVIIa administration (63). However, this result has not been borne out in subsequent studies, with only modest reductions in blood transfusion seen (64–66). Use of rFVIIa in active upper gastrointestinal and variceal bleeding has been associated with an increased thromboembolic risk (67, 68). Given the modest reduction in transfusion with increased risk of thromboembolic events, the use of rFVIIa for the acutely bleeding patient should be limited to rescue therapy for uncontrollable bleeding.

The role of PCC use in liver transplantation and acutely bleeding patients remains to be fully elucidated. It is theorized that the more balanced factor replacement with PCC, as compared to rFVIIa, will allow for coagulopathy correction with lower thromboembolic potential. Safety and efficacy of PCC use in cirrhotic patients undergoing liver transplantation are being investigated (56). Use of any prohemostatic agent during liver transplantation should be balanced against the risk of thromboembolic events, particularly hepatic artery and portal vein thrombosis.

Tranexamic acid decreases transfusion requirements during liver transplantation, but data in spontaneous bleeding episodes are less robust (69). One may consider the use of tranexamic acid when ongoing bleeding is attributed to excess fibrinolysis, as indicated via thromboelastography.

Treatment of acute hemorrhage in patients with liver disease must account for multiple inciting factors outside hemostasis alone. As mentioned previously, renal failure and bacterial infection are known to induce bleeding. These conditions should be addressed as part of the management of all bleeding episodes.

HYPERCOAGULATION AND VENOUS THROMBOEMBOLISM

Just as the balance of hemostasis in patients with liver failure can tilt toward bleeding diatheses, elevated factor VIII levels and relative protein C deficiency frequently lead to hypercoagulopathy and thromboembolic complications. Compared to patients with similar risk factors without cirrhosis, patients with hepatic coagulopathy are equally at risk of deep vein thrombosis, pulmonary embolism, and portal vein thrombosis (70, 71). Routine thromboprophylaxis should not be withheld in this population when risk factors for thromboembolic complications are present, even if routine tests for hemostasis are elevated (72). The anticoagulant agent of choice for thromboembolic prophylaxis in hepatic coagulopathy remains to be determined. It has been suggested that heparin may be less active in these patients, as it relies upon antithrombin to exert anticoagulant action. The levels of antithrombin are often reduced in patients with liver insufficiency. Interestingly, the low molecular weight heparins (LMWHs) are efficacious in patients with cirrhosis at preventing thromboembolic complications (73). Head-to-head comparisons of heparin and LMWHs aimed at evaluating comparable safety and efficacy have not been performed in patients with hepatic insufficiency. As these patients are at elevated risk of both thrombosis and bleeding, careful clinical decision making should guide the use of prophylactic anticoagulants.

Newly diagnosed thromboembolic complications should be treated promptly with anticoagulation. If possible, screening for and eradication of varices prior to initiation of anticoagulation should be attempted. Anticoagulant agent choices include vitamin K antagonists, LMWHs, and newer direct acting oral anticoagulants. Vitamin K antagonists have been associated with increased bleeding risk and can be difficult to monitor in patients with premorbid elevations in INR. Heparin and LMWHs are viable alternatives, especially in the acute setting, as they are able to achieve rapid anticoagulation. The direct acting oral anticoagulants dabigatran, rivaroxaban, and apixaban are promising but clinical experience is limited and dosing adjustments are needed for liver and renal impairment.

CONCLUSIONS

Knowledge of the diverse changes to the hemostatic system in liver disease is growing. Clinicians should be cognizant that traditional measures of coagulopathy are not able to fully characterize the complexity of changes seen in hepatic coagulopathy. The use of prohemostatic agents as prophylaxis against bleeding in the setting of high risk procedures should only be used when benefits of bleeding avoidance outweigh potential thrombotic risks. In the acutely bleeding patient, restrictive transfusion strategies are suggested to avoid potentiating bleeding. Adequate thromboprophylaxis and treatment of thromboembolic events should also be addressed with consideration of patient specific factors.

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