Chapter 2
Coagulopathy in Cirrhosis

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Introduction

Coagulopathy in cirrhosis can be difficult to manage. This chapter will provide a concise, but detailed, overview of the role of the normal and abnormal liver in hemostasis and introduce the concept of rebalanced hemostasis in chronic liver disease. Hepatic production of pro- and antihemostatic proteins in normal and altered hepatic function will be described. Laboratory testing will be discussed, including the effects of chronic liver disease on their interpretation. Finally, bleeding and thrombotic complications, and recommended therapy, will be reviewed.

Physiology of Normal Hemostasis

Appreciating the coagulation abnormalities that occur in liver dysfunction requires a basic understanding of the physiology of normal hemostasis. The process of hemostasis is initiated at the site of injured blood vessels where von Willebrand factor (VWF) binds to subendothelial collagen. Subsequent binding of platelets to VWF results in platelet activation and aggregation. This process is termed primary hemostasis [1]. Concurrently, tissue factor (TF) is released from the endothelium of the damaged vasculature. TF binds to circulating activated factor VII (FVIIa) forming the intrinsic tenase complex, which converts factor X to factor Xa (FXa). FXa proteolytically cleaves a small amount of prothrombin to thrombin. The minimal amount of thrombin generated amplifies the coagulation cascade by activating

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factors VIII (FVIIIa), IX (FIXa), and XI (FXIa), among others. FXIa generates FIXa, which complexes with FVIIIa to form the extrinsic tenase complex. This complex produces large amounts of FXa, which generates enough thrombin to convert fibrinogen to fibrin. Polymerized fibrin monomers are cross-linked by factor XIIIa. This process is referred to as secondary hemostasis and involves a complex interplay among the abovementioned coagulation factors, activated platelets, membrane phospholipids, and calcium for stable clot formation [2].

Unchecked activation of the coagulation cascade may lead to unintended clot formation; therefore, anticoagulant proteins function to ensure that clot formation is limited to sites of vascular injury. The major components of the anticoagulant system are protein C, protein S, antithrombin III (ATIII), and tissue factor pathway inhibitor (TFPI). Protein C, following activation by thrombin bound thrombomodulin, along with protein S – a protein C cofactor, inactivates factors Va and VIIIa [3]. ATIII inactivates factors IXa, Xa, XIa, and XIIa. TFPI limits thrombin generation by inhibiting the TF-FVIIa-FXa complex [4].

Another important component of hemostasis is fibrinolysis. Eventually, fibrinolysis is necessary to prevent excess clot formation. The chief components of the fibrinolytic system are plasmin, tissue plasminogen activator (TPA), alpha-2-antiplasmin, and plasminogen activator inhibitor (PAI). Fibrin-bound plasminogen is converted to plasmin by TPA. Plasmin digests fibrin releasing fibrin degradation products. Regulation of this process is necessary to prevent excess clot breakdown and hemorrhage. Alpha-2-antiplasmin and PAI function in this role and inhibit plasmin and TPA, respectively [5].

Hemostasis in Liver Disease

The liver plays an integral role in hemostasis. Hepatocytes are responsible for the synthesis of the majority of procoagulant, anticoagulant, and fibrinolytic proteins. Liver dysfunction disrupts this process altering the normal hemostatic balance. Historically, liver disease was felt to represent a bleeding diathesis as suggested by the presence of thrombocytopenia and prolongation of the prothrombin time (PT) and activation partial thromboplastin time (aPTT) on routine laboratory tests. More recently, an increasing amount of evidence supports a model of rebalanced hemostasis where concomitant prohemostatic and antihemostatic changes lead to a rebalanced hemostatic system [6–8].

The hemostatic changes that occur in chronic liver disease can be divided into those affecting primary hemostasis (platelet activation), secondary hemostasis (thrombin generation), and fibrinolysis (Table 2.1). Reduced hepatic synthesis of thrombopoietin causes thrombocytopenia and a bleeding tendency. Furthermore, splenic sequestration of platelets in portal hypertension-induced splenomegaly contributes to thrombocytopenia. Alternatively, increased levels of von Willebrand factor, in response to endothelial dysfunction, and decreased production of ADAMTS-13, a VWF cleaving protease, promote platelet adhesion, and hemostasis [9]. Secondary hemostasis is affected by deficiencies of the following procoagulants produced by

Table 2.1 Alterations in hemostasis in chronic liver disease

Phase of hemostasis	Promote hemostasis	Impair hemostasis
Primary hemostasis (platelet activation)	Increased VWF Decreased ADAMTS-13	Thrombocytopenia
Secondary hemostasis (thrombin generation)	Decreased protein C and S Decreased antithrombin III Increased factor VIII	Decreased factors II, V, VII, IX, X, and XI Decreased fibrinogen Dysfibrinogenemia
Fibrinolysis	Decreased plasminogen Increased PAI	Increased tPA Decreased alpha 2-antiplasmian Decreased factor XIII Decreased TAFI

VWF von Willebrand antigen, *ADAMTS-13* a disintegrin and metalloprotease with thrombospondin type 1 motif 13, *PAI* plasminogen activator inhibitor, *tPA* tissue plasminogen activator, *TAFI* thrombin-activatable fibrinolysis inhibitor

the liver: fibrinogen and factors II, V, VII, IX, X, and XI. Additionally, dysfibrinogemia occurs, which promotes bleeding. There is a concurrent decrease in natural anticoagulants, protein C, protein S, and antithrombin III, due to reduced hepatic production, and a marked increase in factor VIII, secondary to endothelial dysfunction. These changes act as drivers of hemostasis [10]. Fibrinolysis is affected in a similar fashion. Decreased plasminogen and elevated PAI promote clot resolution, while increased TPA and reduced alpha-2-antiplasmin inhibit clot breakdown [8].

While the concept of rebalanced hemostasis argues against a hypocoagulable state long believed to be present in chronic liver disease, this balance is far more unstable in comparison to healthy individuals. Multiple factors, such as infection or renal disease, may precipitate bleeding or thrombosis by altering the hemostatic balance in either direction [6].

Clinical Features of Coagulopathy in Liver Disease

One of the most common, and feared, bleeding complications in liver disease is bleeding esophageal varices; however, variceal bleeding is largely related to local vascular abnormalities, including vessel radius, thickness, and pressure, rather than hemostatic disturbances. Vessel pressure is predominantly dictated by splanchnic blood pressure, which is often increased due to hypervolemia, a common problem in liver disease [11]. Other features of bleeding in liver dysfunction include ecchymosis, epistaxis, oral mucosal bleeding, and gastrointestinal bleeding. Further, bleeding can be precipitated by invasive procedures.

Previously, it was assumed liver disease provided protection against thrombosis given the prolonged PT on routine laboratory tests. This now appears to be incorrect. The rate of deep venous thrombosis and pulmonary embolism is anywhere between 0.5 and 8.1% [12]. A more common complication is portal venous thrombosis (PVT), which has a reported prevalence of 11–36% [13]. Portal venous

stasis appears to be the major change in liver disease contributing to the increased risk for PVT [14]. Hypercoagulability (i.e., increased FVIII, decreased protein C, etc.) likely plays a role in clotting when the hemostatic balance is tipped in the favor of thrombosis. The prevention and treatment bleeding and thrombotic complications in chronic liver disease will be discussed later.

Coagulation Tests in Liver Disease

No one test can accurately predict the risk of bleeding in liver disease (Table 2.2). Two of the most commonly used tests are the PT and aPTT, which measure the time to formation of a fibrin clot. While inexpensive and widely available, both gauge just one aspect of coagulation and are not predictive of bleeding in chronic liver disease [15]. Similarly, obtaining a platelet count is another common test to evaluate bleeding risk. A platelet count less than 50,000/μL confers an increased risk of bleeding with invasive procedures in liver disease; however, higher platelet counts

Table 2.2 Diagnostic tests to measure hemostasis in chronic liver disease

Name of test	Comments
Platelet count	Widely available, timely results, and inexpensive
	Predicts risk of bleeding only at extreme levels
	Does not indicate platelet function
PT/INR	Widely available, timely results, and inexpensive
	Correlates with severity of liver disease but does not predict risk of bleeding in chronic liver disease
	Measures narrow aspect of procoagulant system
	High interlaboratory variability
aPTT	Widely available, timely results, and inexpensive
	Often normal in chronic liver disease
	Measures narrow aspect of procoagulant system
Coagulation factor activity	Does not correlate with risk of bleeding or thrombosis
	Not widely available
	High interlaboratory variability
Fibrinogen	Acute phase reactant
	Does not correlate with risk of bleeding in chronic liver disease
Thromboelastography	Global measure of hemostasis that can detect multiple perturbations in coagulation
	Rapid results
	Requires expertise in interpretation
	Not validated for predicting risk of bleeding or thrombosis in nonsurgical patients
Endogenous thrombin potential	Better representation of pro- and anticoagulant balance
	Not validated
	Experimental

do not appear to predict bleeding risk [16]. Various other less commonly used laboratory tests are employed. Fibrinogen is a measure of the fibrinolytic system and decreased levels are indicative of fibrinolysis; however, fibrinogen is not correlated with bleeding risk in liver disease [16].

A major disadvantage of the above tests is their inability to assess more than a single aspect of the hemostatic system, which is less than ideal in chronic liver disease, a disorder with multiple perturbations of hemostasis. Global tests of hemostasis, such as thromboelastography (TEG), are methods of measuring whole-blood coagulation. TEG is often used perioperatively by surgeons and anesthesiologists. Given the numerous abnormalities present in liver disease, many acting in opposition to one another, tests such as TEG, may provide a more accurate assessment of bleeding risk. Indeed, TEG has been shown to be useful in detecting coagulopathy in liver disease [17]. Another global measure of hemostasis, the thrombin generation assay measures thrombin production and may be beneficial when evaluating coagulopathy in liver dysfunction. Thrombin generation is often normal or increased in liver disease, which highlights the concept of rebalanced hemostasis previously mentioned [18]. Thrombin generation assays are still experimental and may provide a more accurate measure of bleeding and thrombotic risk in chronic liver disease but further study is needed.

Management of Bleeding in Liver Disease

A variety of options are available for the treatment and prevention of bleeding in chronic liver disease (Table 2.3). Prevention of bleeding is a concern in certain high-risk patients and prior to invasive procedures.

Table 2.3 Treatment options for chronic liver disease related coagulopathy

Type of product	Comment
Red blood cells	Transfusions should be administered to maintain minimally acceptable hemoglobin threshold depending on the clinical situation
Platelets	Reserved for severe thrombocytopenia or platelet count less than 50,000/μL with active bleeding
Fresh frozen plasma	Reserved for active bleeding
	Large volume (20–40 mL/kg) necessary for correction of coagulation factor deficiencies and may result in volume overload
	Not recommend for bleeding prevention prior to invasive procedures
Cryoprecipitate	Reserved for active bleeding with hypofibrinogenemia
Transexamic acid	Administered in patients with hypofibrinogenemia
Desmopressin	May improve platelet function but no data regarding efficacy in chronic liver disease
Prothrombin complex concentrates and recombinant factor VIIa	Reserved for severe and/or refractory bleeding
	Risk of thrombosis
	Expensive
	Limited data regarding efficacy in chronic liver disease

One of the most commonly encountered bleeding complications experienced in liver disease is esophageal variceal bleeding. As previously mentioned, the etiology of variceal bleeding is related to local vascular abnormalities, such as splanchnic blood pressure, rather than abnormalities of hemostasis. Thus, treatment is not necessarily directed at correcting hemostatic abnormalities; however, as is the case with all potentially life-threatening bleeding events, volume resuscitation with red blood cells is critical. The goal hemoglobin concentration is 7–8 mg/dL [19]. It is important to avoid excessive transfusion since excess volume can increase splanchic portal pressure and further exacerbate bleeding. The key treatment modality in acute variceal bleeding is endoscopic variceal banding or ligation. While not the mainstay of treatment, correction of hemostatic defects is frequently attempted prior to invasive procedures, such as endoscopic therapy, to prevent worsened bleeding. Other potential bleeding complications that may arise in chronic liver disease include portal hypertensive gastropathy or gastric vascular ectasia-related bleeding and bleeding associated with invasive procedures. Commonly performed invasive procedures in liver dysfunction include percutaneous or transjugular liver biopsy, abdominal paracentesis, and accessing vascular sites (i.e., central venous catheter placement), among others.

Various blood products and hemostatic agents are administered for the treatment and prevention of bleeding in liver disease. Red blood transfusions to replace blood loss have already been discussed. The others are aimed at improving underlying hemostatic defects. Fresh frozen plasma (FFP) contains both pro- and anticoagulation factors and can be administered to replace deficiencies of either. FFP is most commonly administered to correct a prolonged PT. The efficacy of FFP to prevent bleeding has never been demonstrated [20]. Moreover, the volume of FFP necessary to correct coagulation factor deficiencies is large – 20–40 mL/kg – and complete correction is seldom accomplished [21, 22]. Potential adverse effects include pulmonary edema and increased portal venous blood pressure, among others. Therefore, in chronic liver disease, FFP is not recommend for the prevention of bleeding in patients with a prolonged PT prior to invasive procedures, and its use in actively bleeding patients is questionable. Platelet transfusions are often administered for thrombocytopenia. Adequate thrombin production occurs with a platelet count greater than 50,000/μL. Transfusion to obtain this value is warranted in active bleeding and should be considered for prophylaxis prior to invasive procedures [23–25]. In some instances, it may be difficult to achieve a platelet count of 50,000/μL or greater due to splenic sequestration of platelets in portal hypertension-induced splenomegaly, often present in liver disease. Cryoprecipitate, which contains fibrinogen and coagulation factors V and VIII, should be administered in bleeding patients with hypofibrinogenemia until fibrinogen levels normalize [26]. Its use as a prophylactic agent to prevent hemorrhage is not well studied. Similarly, when hyperfibrinolysis is a concern, antifibrinolytic agents, such as tranexamic acid, may be used. Last, recombinant factor VIIa (rFVIIa) and prothrombin complex concentrates (PCC) represent low-volume prohemostatic alternatives to FFP. Recombinant FVIIa has not been shown to be beneficial in bleeding esophageal varices or with prophylactic use prior to liver transplantation [27]. Therefore, routine use is not recommended

except during very high-risk procedures, such as intracranial pressure monitor placement and rescue therapy for refractory, life-threatening bleeding. There are limited data regarding the use of PCCs in similar situations, so it cannot be recommended for routine use either. Adverse effects of both therapies include thrombogenicity, high expense, and need for frequent therapy.

Management of Thrombosis in Liver Disease

Although liver disease was formerly believed to represent a bleeding diathesis, thus providing protection from thrombotic events, it is now known that this is not true. The precarious nature of the pendulum in rebalanced hemostasis in chronic liver disease can swing in the direction of bleeding or clotting. Despite the presence of thrombocytopenia and an elevated INR, termed autoanticoagulation, a misnomer, deep venous thrombosis (DVT) and pulmonary embolism (PE) do occur and affected patients should receive anticoagulation.

Deciding which anticoagulant to recommend can be difficult in chronic liver disease. Often, the INR is already elevated due to reduced hepatic synthesis of coagulation factors. Therefore, the addition of oral vitamin K antagonists (VKA) is problematic because it is challenging to determine if the INR value is due to liver disease or related to VKA use and it may not be possible to determine the INR range that represents therapeutic anticoagulation. Furthermore, the interlaboratory variability in INR is unacceptably high [28]. A more appropriate choice of therapy may be low molecular weight heparin (LMWH) since it does not require INR monitoring, although it presents potential difficulties too. LMWH functions by enhancing ATIII activity, which is often reduced in liver disease. This may result in unpredictable efficacy and necessitate anti-Xa level monitoring to ensure therapeutic dosing; however, anti-Xa levels may not be completely reliable. Despite subtherapeutic anti-Xa levels, thrombin generation assays have shown reduced thrombin generation in patients with chronic liver disease indicative of an increased responsiveness to LMWH in liver disease [29]. Limited data are available on the use of direct oral anticoagulants to treat venous thromboembolism in chronic liver disease; therefore, their efficacy and safety are uncertain for now and cannot be recommended.

PVT is the most common thrombotic complication experienced in chronic liver disease and is more often related to portal venous stasis rather than hypercoagulability. Clinical data from randomized clinical trials regarding the optimal treatment of PVT in cirrhosis are lacking; thus, the American Association for the Study of Liver Disease neither recommends for or against anticoagulation. Despite this shortcoming, there are a limited number of nonrandomized clinical studies demonstrating the efficacy and safety of VKA and LMWH. The goal of anticoagulation in PVT is recanalization of the obstructed blood vessel and decreasing the risk of extension to the superior mesenteric vein (SMV) to prevent intestinal ischemia and reduce portal hypertension. Exactly who should receive treatment is uncertain. Generally,

anticoagulation is recommended for liver transplantation candidates since PVT is associated with decreased survival in patients undergoing liver transplantation. Patients not eligible for liver transplantation should receive anticoagulation on an individualized basis. The presence of PVT extension into the SMV or a coexisting thrombophilia usually warrants anticoagulation [30]. Successful recanalization occurs anywhere from one-third to nearly one-half of the time in patients receiving LMWH and VKA, respectively [31]. Initiation of anticoagulation within 6 months of PVT diagnosis is associated with a higher rate of recanalization [32]. Importantly, since bleeding in liver disease is most commonly related to portal hypertension, esophageal varices should be treated prior to beginning anticoagulation. Patients with prior variceal bleeding, large varices, and no history of bleeding, or small varices and a high risk of bleeding should undergo endoscopic therapy or begin treatment with a nonselective beta blocker [33]. The optimal duration of anticoagulation in PVT and cirrhosis is uncertain. Most studies treated the subjects for 6 months. If complete recanalization is not present at 6 months, a more prolonged duration of anticoagulation may still result in successful resolution of thrombosis [34]. Given the high rate of recurrent PVT following anticoagulation cessation, a longer duration of therapy to prevent recurrent thrombosis may be warranted in liver transplantation candidates and individuals with underlying thrombophilia. Other therapeutic options for PVT include thrombolysis and transjugular intrahepatic portosystemic shunt (TIPS). Limited evidence is available regarding the use of thrombolysis in PVT, but it may be advantageous in intestinal ischemia or anticoagulation failure. A considerable more amount of evidence is available for the use of TIPS in PVT, and it may serve a role in failure or contraindication of anticoagulation [35].

Several studies have shown the risk of VTE in hospitalized patients with chronic liver disease is no lower than hospitalized noncirrhotic patients, and in fact, may be greater [36–38]. Despite the risk of thrombosis in chronic liver disease, patients often do not receive thromboprophylaxis during hospitalization [39, 40]. This is likely related to a fear of bleeding and the inappropriate assumption that a prolonged INR in liver disease is protective against clotting. While not specifically addressed in the most recent consensus guidelines, accumulating data are leading to an increasing amount of evidence to support thromboprophylaxis in hospitalized patients with chronic liver disease [41].

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