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Hemostatic Defects in End Stage Liver Disease

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The liver has a pivotal role in hemostasis by synthesizing all clotting factors (except von Willebrands factor) and coagulation inhibitors as well as several fibrinolytic proteins. The hepatic reticuloendothelial system clears activated clotting factors, proteolytic enzyme/inhibitor complexes, and fibrin and fibrinogen degradation products. End stage liver disease (ESLD) results in a complex and variably severe failure of hemostasis that may predispose to abnormal bleeding. The diverse spectrum of hemostatic defects includes impaired synthesis of clotting factors, excessive fibrinolysis, disseminated intravascular coagulation, thrombocytopenia, and platelet dysfunction (Table 1). This article reviews the hemostatic defects that occur in ESLD with a focus on laboratory diagnosis and treatment.

Coagulation defects

The progressive loss of hepatic parenchymal cells results in clotting factor deficiencies. The importance of the coagulopathy is underscored by the incorporation of coagulation parameters into prognostic scores for fulminant hepatic failure and cirrhosis, and their use for assessing bleeding risk [1]. Clotting factor deficiencies primarily reflect impaired hepatic synthetic function, although increased consumption and extravascular re-distribution may also contribute. The number and degree of clotting factor deficiencies parallels the severity of liver damage [2]. Several studies demonstrated the progressive loss of hepatocytes expressing several clotting factors with more advanced liver disease

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Table 1
Hemostatic defects in ESLD

Hemostatic defect	Possible mechanisms
Impaired coagulation	Reduced synthesis of clotting factors
	Vitamin K deficiency
	Dysfibrinogenemia
Systemic fibrinolysis	Impaired clearance of tPA and fibrinolytic enzymes
	Reduced synthesis of α_2-antiplasmin and TAFI
	Reabsorption of ascitic fluid into circulation
Thrombocytopenia	Sequestration due to splenomegaly
	Impaired synthesis of thrombopoietin
	Immune destruction
	DIC
	Other (drugs, folate deficiency, alcohol)
Platelet function defects[a]	Circulating platelet inhibitors
	Excess nitric oxide production
	Deficiency of platelet glycoprotein receptors
	Defective platelet signal transduction
	Altered membrane phospholipid composition
	Impaired thromboxand A_2 synthesis
Disseminated intravascular coagulation	Release of procoagulants from injured hepatocytes
	Impaired clearance of activated clotting factors
	Reduced synthesis of coagulation inhibitors
	Endotoxins in portal circulation
	Entry of ascitic fluid into systemic circulation

Abbreviations: DIC, disseminated intravascular coagulation; TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue plasmingen activator.

[a] None of these defects occur consistently in ESLD.

[2,3]. Factor (F)V and FVII levels are sensitive indicators of hepatic protein synthesis often used to assess the severity of disease [4,5]. FVII is the first clotting factor level to fall, because of its short half-life of 6 hours. FVII deficiency develops in 75%–85% of patients, and levels range from 23% to 74% of normal in compensated cirrhosis [4,6,7]. FVII levels are significantly lower in decompensated cirrhosis, but are >30% of normal in most patients with stable disease [4,5,8]. The levels of FV, FX and prothrombin usually fall in parallel with the progression of liver disease, although clotting factor levels vary considerably, and range from 10% to >110% of normal [5,8–11]. In contrast, FVIII and fibrinogen levels are normal or increased in most patients with stable cirrhosis [7,8,10]. Elevated FVIII levels are not caused by increased gene transcription and may reflect the parallel increase in von Willebrand factor (vWF) levels in cirrhosis [3]. Fibrinogen is an acute phase reactant, and synthesis is conserved in patients with stable disease.

An acquired dysfibrinogenemia develops in 50%–78% of patients with ESLD [12–14]. The increased sialic acid content of the abnormal fibrinogen impairs polymerization of fibrin monomers [15]. A dysfibrinogenemia is suggested by a prolonged thrombin time in the absence of elevated fibrin degradation products

(FDP) or D-dimer levels. The level of clottable fibrinogen may be low with a functional assay, but the fibrinogen protein level will be normal using an immunologic assay. The clinical significance of the dysfibrinogenemia of ESLD is unclear, but unlikely to cause bleeding in most patients.

Vitamin K is a required cofactor for gamma-carboxylation of glutamic acid residues on prothrombin, FVII, FIX, FX, protein C, and protein S, a modification required for binding to phospholipid surfaces. Vitamin K deficiency occurs commonly in ESLD as a result of poor nutrition, malabsorption of fat soluble vitamins, or biliary tract obstruction. Cirrhotic patients also develop an acquired defect of gamma carboxylation unresponsive to vitamin K, which is reflected by increased levels of hypocarboxylated vitamin K- dependent clotting factors [16].

The risk of bleeding associated with the coagulopathy of ESLD depends on the number and severity of clotting factor deficiencies. Individual clotting factor levels often remain in a hemostatically effective range in patients with stable disease. In contrast, patients with the more severe and complex hemostatic defects characteristic of decompensated cirrhosis are at risk for spontaneous and procedure-related bleeding. However, individual clotting factor levels do not reliably predict bleeding or survival [17,18].

Systemic fibrinolysis

Laboratory evidence of low grade systemic fibrinolysis is found in 30% – 46% of patients with ESLD [19–21]. Fibrinolytic acitivity increases with the progression of liver disease, but varies considerably between individuals [18,19,21–23]. Accelerated fibrinolysis results from the impaired clearance of tissue plasminogen activator (tPA) and other fibrinolytic enzymes by the diseased liver, without an appropriate increase in plasminogen activator inhibitors [21,22,24]. Impaired hepatic synthesis of fibrinolytic inhibitors (α_2 anti-plasmin and thrombin-activatable fibrinolysis inhibitor [TAFI]) contributes to the increase in circulating plasmin. TAFI removes C-terminal lysine residues on fibrin, which serve as binding sites for the activation of plasminogen. TAFI levels are markedly reduced in patients with cirrhosis and correlate with the severity of disease [25–27]. Reabsorption of ascitic fluid into the systemic circulation may contribute to accelerated fibrinolyisis in some cases [28].

The clinical significance of systemic fibrinolysis varies between individuals and with the severity of liver disease. Low grade fibrinolysis probably does not markedly increase the bleeding risk in most patients with stable disease. Up to 30% of patients with compensated cirrhosis have laboratory evidence of accelerated fibrinolysis without clinically significant bleeding [19,23]. However, patients with liver disease often have an exaggerated fibrinolytic response to physiologic and iatrogenic stresses, especially surgery [24,29–31]. Major surgery may stimulate the release of large amounts of tPA from injured tissues, tem-

porarily overwhelming antifibrinolytic mechanisms and resulting in a "burst" of fibrinolysis and bleeding [32]. Premature lysis of hemostatic plugs at vascular injury sites may provoke or exacerbate bleeding. Systemic fibrinolysis was associated with soft tissue, variceal and surgical bleeding in some [20,21,23, 32–34] but not all studies [18,34]. Bleeding can occur anywhere, but is particularly prominent at sites of trauma or surgery. Affected patients often develop generalized oozing from surgical incisions and venipuncture sites, occasionally severe and refractory to therapy [35].

Systemic fibrinolysis should be suspected in patients with persistent bleeding despite optimal clotting factor and platelet replacement. The diagnosis is suggested by a shortened euglobulin clot lysis time, which reflects circulating fibrinolytic enzymes. An elevated D-dimer level indicates plasmin lysis of cross-linked fibrin when fibrinolysis is secondary to the activation of coagulation. Severe fibrinolysis often results in a substantial fall in fibrinogen and $\alpha_2$antiplasmin levels, due to consumption as well as impaired synthesis.

Thrombocytopnia

Mild to moderate thrombocytopenia occurs in 49% –64% of patients with ESLD [36,37]. However, the platelet count is rarely less than 30, 000 to 40,000 and spontaneous bleeding is uncommon. The etiology of thrombocytopenia is multifactorial, and includes sequestration of platelets in an enlarged spleen, impaired platelet production, and immune and non-immune mediated platelet destruction. Other causes such as folate deficiency, alcohol, sepsis, disseminated intravascular coagulation (DIC), and drugs may also contribute in individual cases.

Radiolabled platelet studies demonstrate splenic sequestration in ESLD. The spleen normally contains approximately one-third of the total platelet mass, exchanging with circulating platelets [38]. In contrast, a markedly enlarged spleen may sequester up to 90% of the total platelet mass [38–40]. Platelet counts correlated inversely with spleen size in some [41–44] although not all studies [45–48]. "Hypersplenism" is thought to reflect an exaggeration of the normal function of splenic macrophages to remove senescent cells. In one study, platelet counts correlated inversely with the number of phagocytically active splenic macrophages, supporting their role in the pathogenesis of thrombocytopenia [49]. There is conflicting data on platelet lifespan in ESLD, with decreased survival reported in some [40,45,46] but not all studies [38,39].

Although it contributes in some cases, other evidence argues against splenic sequestration as the primary cause of thrombocytopenia in ESLD. Portal decompression procedures and splenectomy do not consistently improve platelet counts [37,50–55]. Thrombocytopenia occurs in nearly 25% of cirrhotic patients with normal spleen size, suggesting other mechanisms must be involved [42,48,56]. Conversely, 19%–29% of cirrhotic patients with splenomegaly maintain normal platelet counts, suggesting splenic pooling alone is not sufficient to cause

thrombocytopenia [42,56]. Flow cytometric analysis of young reticulated platelets in peripheral blood is a useful indicator of platelet production. Reticulated platelet counts are significantly lower in cirrhotic patients with thrombocytopenia than in those with normal platelet counts, implicating impaired thrombopoiesis [57,58].

Thrombopoietin (TPO), the priniciple physiologic regulator of platelet production, is synthesized constitutively in the liver [59]. There is accumulating evidence that impaired hepatic synthesis of TPO is a major cause of thrombocytopenia in liver disease. Thrombocytopenic patients with ESLD have inappropriately low TPO levels [43,44,57,60–63]. TPO levels are significantly lower in cirrhotic patients with thrombocytopenia than in those with normal platelet counts [41,47,58]. Patients with splenomegaly and normal platelet counts have significantly higher TPO levels than those with thrombocytopenia, which suggests that higher TPO levels result in a compensatory increase in platelet production [42]. Serum TPO levels correlate inversely with the severity of liver disease reflected by the degree of fibrosis, Child Pugh class, and sensitive measures of liver function [41–43,48]. TPO mRNA levels are significantly reduced in cirrhotic liver tissue [60,61]. Replacement of a cirrhotic liver with a functional graft restores TPO production and corrects thrombocytopenia [47,60,62–64]. The consistent increase in TPO levels and platelet count after orthotopic liver transplantation strongly implicates impaired TPO production as a primary cause of thrombocytopenia [47,62,63,65].

Elevated levels of platelet-associated IgG are found in 55%–88% of patients with chronic liver disease [44,66–70], and correlates inversely with the platelet count in some [44,68,70] but not all studies [66]. However, platelet associated IgG does not confirm immune-mediated platelet destruction, since high levels occur in liver disease patients with normal platelet counts and non-immune thrombocytopenia [66,69]. More specific autoantibodies directed against the most common platelet glycoprotein antigenic targets in idiopathic thrombocytopenic purpura (ITP) are found in 38%–64% of patients with liver disease [66,71]. There is some evidence that immune mediated thrombocytopenia is more frequent in patients with hepatitis C-associated liver disease [68,71,72]. Anti-platelet glycoprotein autoantibodies are more common in patients with chronic hepatitis C than those with ESLD due to other etiologies [71,72]. Patients with chronic hepatitis C have an increased frequency of ITP, consistent with the propensity for autoimmune complications [72–75]. Reports of response to standard immunologic therapies (corticosteroids, intravenous immunoglobulin [IVIG]) support immune-mediated thrombocytopenia in some cases [72–75].

The available evidence suggests impaired TPO production caused by the progressive loss of functioning hepatocytes, is a primary cause of thrombocytopenia in ESLD. However, the widely variable extent of splenic sequestration, TPO levels, platelet survival, and unpredictable effect of portal decompression procedures, suggest different mechanisms predominate in different patients [40,46,50,53]. It is unknown whether the etiology of thrombocytopenia affects the risk of bleeding.

Platelet function defects

Qualitative platelet abnormalities occur in patients with ESLD, reflected by a prolonged bleeding time, and impaired platelet aggregation responses to multiple agonists. The bleeding time is prolonged in 40% of patients with cirrhosis and correlates with the severity of disease, reflected by Child-Pugh class and laboratory parameters [76–79]. Abnormal bleeding times are only partly explained by thrombocytopenia, since they occur in 12%–25% of cirrhotic patients with normal platelet counts [76–78]. The platelet function analyzer (PFA-100) is an in vitro system for evaluation of platelet-dependent primary hemostasis. Although abnormal PFA-100 results occur in patients with ESLD, its use in this population has not been well studied [80].

Impaired platelet aggregation in vitro is found in 46% of patients with cirrhosis, although the pattern of abnormalities is not consistent [80–82]. Abnormal platelet function has been attributed to circulating platelet inhibitors (FDP and D-dimers), plasmin degradation of platelet receptors, dysfibrinogenemia, and excess nitric oxide synthesis [77,78,81–84]. Nitric oxide is a powerful vasodilator and inhibitor of platelet adhesion and aggregation produced by vascular endothelial cells. Inhibition of nitric oxide production normalized prolonged bleeding times in a rat model of cirrhosis [83]. A variety of intrinsic platelet defects are also reported including a deficiency of platelet GPIb receptors, defective signal transduction, impaired thromboxane A_2 synthesis, altered membrane phospholipid composition, and acquired storage pool deficiency [85–87]. However, none of these defects occur consistently, which suggests a multifactorial etiology involving both intrinsic and extrinsic factors.

Disseminated intravascular coagulation

Patients with ESLD often have evidence of chronic low grade DIC. Fibrinogen survival is reduced and elevated levels of various markers of coagulation activation are found in plasma [40]. Multiple studies demonstrated elevated levels of the prothrombin activation fragment F1 + 2, Fibrinopeptide A, D-dimer, and thrombin-antithrombin complexes, although values vary markedly between patients [88–93]. The infusion of heparin lowered the level of coagulation activation markers and prolonged fibrinogen survival, confirming accelerated intravascular coagulation [40,91]. The frequency and severity of DIC correlate with the stage of liver disease in most studies [88,89,93,94]. Elevated levels of D-dimers and F1 + 2 are found in up to 93%–100% of patients with advanced stage cirrhosis and complications such as ascites [28,89]. In contrast, laboratory evidence of DIC is found in a minority of patients with compensated cirrhosis [93,95,96].

The mechanisms triggering DIC in ESLD are complex and include release of procoagulants from injured hepatocytes, impaired clearance of activated clotting factors, reduced synthesis of coagulation inhibitors, and entry of endotoxins into the portal circulation. The severity of DIC is inversely related to antithrombin and

protein C levels, and antithrombin replacement prolongs fibrinogen survival [88,90,97]. Plasma levels of tissue factor are elevated in patients with advanced cirrhosis and correlate with the severity of disease [98]. Endotoxinemia is strongly associated with high plasma levels of F1 + 2 and D-dimer, implicating it as a trigger of coagulation activation [89]. The entry of procoagulant-rich ascitic fluid into the systemic circulation may also contribute, explaining the development of DIC after peritoneal-venous shunt placement.

Because of the similar hemostatic defects and pattern of laboratory abnormalities, the diagnosis of DIC in ESLD is difficult, and its clinical significance is often unclear. DIC is more likely in patients with coexisting conditions independently associated with accelerated intravascular coagulation, such as sepsis, or trauma. Classic laboratory tests for DIC are often abnormal in ESLD, but may reflect other hemostatic defects. However, the pattern of testing is often useful for identifying superimposed DIC. D-dimer (and FDP) levels are usually much higher in DIC. An elevated D-dimer level is a more specific marker of DIC since it indicates activation of both coagulation and fibrinolyisis. In contrast, high FDP levels may reflect fibrinogen degradation products or cross-reacting dysfunctional fibrinogen, both common in ESLD [96]. Because fibrinogen synthesis is conserved in compensated cirrhosis, low levels (< 100–120 mg/dL) suggest DIC. Serial testing demonstrating declining FVIII and fibrinogen levels with an elevated D-dimer level in an appropriate clinical setting provides strong presumptive evidence for DIC.

Thrombosis

The balance between the levels of procoagulant and anticoagulant proteins determines the overall effect on hemostasis and resulting risk of hemorrhage and thrombosis. Although bleeding occurs more frequently, the hemostatic imbalance in ESLD occasionally favors hypercoagulability, predisposing to thrombosis. Deficiencies of anticoagulation proteins are common, and correlate with the severity of disease [13,18,26,88,90,99]. Antithrombin, protein C and protein S levels range from 30% to 65% of normal, similar to the range of values found in patients with inherited deficiencies [18,26,95,99]. The high levels of several procoagulant factors in cirrhosis (FVIII, vWF and fibrinogen) may contribute to hypercoagulability [100]. Cirrhotic patients with prothrombotic risk factors superimposed on an already activated coagulation system are at risk for thrombotic complications. There is some evidence that thrombophilic disorders increase the risk of thrombosis in patients with ESLD [99,101]. Cirrhotic patients with the prothrombin gene mutation have a nearly sixfold increased risk of portal vein thrombosis [101]. Cirrhotic patients with a prolonged PT are not necessarily ‘‘auto-anticoagulated’’ and therefore protected from thrombosis. Therapeutic warfarin lowers the levels of all four vitamin K-dependent clotting factors (FII, FVII, FIX, FX) to 15%–30% of normal. In contrast, patients with ESLD often have low FVII levels with relatively higher FIX, FX and prothrombin levels in

the 40%–60% range [7,9,11,102]. Because lower levels of prothrombin and FX are required for an effective anti-thrombotic effect, the coagulopathy of ESLD does not necessarily prevent thrombosis [103].

A variety of thrombotic complications occur in patients with ESLD. An autopsy series found thrombi in one or multiple organs in 54% and 22% of patients with cirrhosis, respectively [104]. Hepatic vein thrombosis is common in cirrhosis and is implicated in disease progression [105]. Thrombotic risk factors are independently associated with the extent of hepatic fibrosis, which suggests that vascular obstruction may accelerate its development [106]. Portal vein thrombosis occurs in 9% – 20% of patients with cirrhosis, and is more frequent in those with advanced disease [101,104,107,108]. Cirrhotic patients have biochemical evidence of hypercoagulability in the portal circulation, which may predispose to thrombosis in this particular location [109].

Laboratory tests

Standard screening tests are used to assess the hemostatic derangement in patients with liver disease who are actively bleeding or require invasive procedures (Table 2). Initial testing should include a PT/INR, aPTT, platelet count, and fibrinogen level. These tests provide a measure of liver disease severity and serve as a baseline for monitoring blood product replacement. In selected patients, a D-dimer, euglobulin clot lysis time, thrombin time, and PFA-100 (or bleeding time) may provide additional useful information (Table 2). Clotting times typically remain in the normal range until clotting factor levels

Table 2
Typical laboratory results in ESLD

Condition	Laboratory findings
Compensated ESLD	PT/INR prolonged
	aPTT prolonged
	Fibrinogen normal or decreased
	Platelet count normal or decreased
Systemic fibrinolysis	Fibrinogen normal or decreased
	Euglobulin Clot Lysis Time shortened
	D-dimer increased
	α_2-antiplasmin decreased
Dysfibrinogenemia	Clottable fibrinogen decreased[a]
	Fibrinogen antigen normal[b]
	Thrombin Time prolonged
Disseminated intravascular coagulation	Fibrinogen normal or decreased[c]
	Platelet count decreased
	D-dimer increased
	FVIII normal or decreased[c]

[a] Using a functional assay of clottable fibrinogen.
[b] Using an immunologic assay of fibrinogen protein.
[c] Declining levels on serial testing suggests DIC.

are less than 30%–40% of normal. A prolonged PT/INR with a normal aPTT occurs in mild liver disease, indicating an isolated deficiency of FVII, which affects only the PT. With disease progression the PT/INR and aPTT are both prolonged, reflecting deficiencies of multiple clotting factors. However, prolongation of the aPTT may be blunted by the high FVIII levels common in compensated cirrhosis [110]. There is no definitive evidence that individual clotting factor levels are more predictive of bleeding or prognosis, although they may be useful in specific circumstances.

The fibrinogen level is normal or elevated in patients with stable chronic liver disease. Severe hypofibrinogenemia (<100 mg/dL) is uncommon, but occurs in decompensated cirrhosis or DIC. Fibrinogen levels <80 mg/dL markedly prolong the PT and PTT, caused by the resulting inability to form a detectable fibrin clot, which is the endpoint of these assays. The thrombin time is prolonged by hypofibrinogenemia, dysfibrinogenemia, or elevated levels of fibrin/fibrinogen degradation products and D-dimers.

The diagnosis of ITP is suggested by thrombocytopenia disproportionate to the severity of liver disease, and is confirmed by a response to immunosuppression. An elevated peripheral blood reticulated platelet count occurs with ITP and other causes of increased platelet destruction. A prolonged bleeding time or abnormal PFA-100 out of proportion to thrombocytopenia suggests platelet dysfunction, although neither test reliably predicts bleeding [79].

International normalized ratio in ESLD

The international normalized ratio (INR) system was developed to standardize PT reporting for patients on stable oral anticoagulation. Its validity for reporting PT values in ESLD has not been confirmed. Several studies demonstrated significantly different INR values with different thromboplastin reagents in patients with liver disease, especially at high INR values [9,111]. The variable results with different thromboplastins suggest INR values may not accurately reflect the coagulopathy in ESLD. Depending on the sensitivity of the thromboplastin, the INR may over- or underestimate the severity of liver disease, potentially affecting clinical prognostic scores.

The INR is calculated from the PT ratio (patient PT/control PT) adjusted for the international sensitivity index (ISI). The ISI reflects the sensitivity of a particular thromboplastin to a reduction in vitamin K-dependent clotting factors, and is derived from a cohort of patients on stable vitamin K antagonists. However, the INR in liver disease does not reflect the same pattern of clotting factor deficiencies found in patients on oral anticoagulation. Patients with ESLD typically have lower FV and fibrinogen levels and higher FX and prothrombin levels than patients on warfarin with similar INR values [5,9]. In one study, liver disease patients had significantly lower FV and FVII levels for a given increment in INR than warfarin-anticoagulated controls [5]. Thus, a particular INR value does not

necessarily reflect the same degree of ''auto-anticoagulation'' or bleeding risk in liver disease as in patients receiving warfarin.

Treatment

Correction of hemostatic defects is required in patients who are actively bleeding or who require surgery or other invasive procedures (Table 3). The therapeutic approach should be tailored to the type, site, and severity of bleeding. Since the most common cause of bleeding in ESLD is a localized anatomic defect, the evaluation should focus on identifying the site of bleeding. Correction of hemostatic defects should be coordinated with definitive therapy to the bleeding site, such as sclerotherapy of bleeding varices. Serial hemostasis laboratory tests are used to monitor the response to therapy. Therapy should be aimed at achieving hemostatic competence rather than complete correction of abnormal laboratory values.

Coagulopathy

Vitamin K

Coagulation screening tests do not distinguish between vitamin K deficiency and clotting factor deficiencies caused by impaired hepatic synthesis. Thus, a trial of vitamin K is useful, especially in patients with cholestatic liver disease. Although vitamin K deficiency is rarely the primary cause of a coagulopathy, a brief course of vitamin K (5 –10 mg/d for 3 days) will exclude it as a contributing factor.

Plasma

Fresh frozen plasma (FFP) contains all coagulation proteins (except vWF) and inhibitors present in circulating blood. FFP is administered to correct coagulation

Table 3
Treatment of hemostatic defects in actively bleeding patients with ESLD

Laboratory parameter[a]	Treatment
INR >2.0 (with normal aPTT) or aPTT >1.3 × control	Fresh frozen plasma ?Recombinant factor VIIa
Fibrinogen <125 mg/dL	Cryoprecipitate
Platelet count <50,000–75,000/mL	Platelet transfusion
Prolonged bleeding time or prolonged closure time on PFA-100[b]	?DDAVP Red cell transfusion if Hct <30%

Abbreviations: DDAVP, desmopressin; Hct, hematocrit; PFA-100, platelet function analyzer.

[a] Serial testing used to monitor response to therapy.

[b] See text for details.

defects before invasive procedures and to control active bleeding. However, correction of the coagulopathy of ESLD is difficult, due to the short half-life of several clotting factors and the large volumes required. Several studies showed that infusion of 2–6 units of FFP corrected a prolonged PT in only a minority (12% – 36%) of patients with chronic liver disease [112–114]. Although larger volumes are more effective, complete correction does not occur in at least 25% of patients [114,115]. The duration of effect is transient; PT values return to baseline within 24 hours in the majority of cases [115,116]. Thus, repeated transfusions every 8 –12 hours are usually required to maintain a near normal PT. FFP is variably effective in increasing individual clotting factor levels, depending on the severity of coagulopathy and volume infused. Although hemostatically effective levels are achieved in most cases, the effect is transient, especially for FVII [112,113,115,116].

There are no controlled trials confirming the efficacy of FFP for prophylaxis or treatment of bleeding in ESLD. There is currently no consensus on the severity of coagulopahy or specific invasive procedures that mandate prophylactic FFP infusions. The volume of FFP required to prevent or treat bleeding is also unknown, and likely varies with the severity of coagulopathy and clinical setting. Replacement therapy should be directed at achieving hemostatically effective clotting factor levels rather than normalization of coagulation screening tests. For example, an isolated mild FVII deficiency (reflected by a prolonged PT and normal aPTT) is unlikely to cause bleeding in the absence of coexisting hemostatic defects. Since FVII levels >15% of normal are adequate for hemostasis in patients with an inherited deficiency, an isolated mildly prolonged PT/INR does not require plasma infusions [117]. The minimum level of clotting factors required for hemostasis in patients with multiple coagulation defects is not well-defined. Large volumes of plasma are poorly tolerated by patients with ESLD, who usually already have an expanded intravascular volume. Volume overload may precipitate congestive heart failure or increase portal pressure, with the risk of variceal rupture. Other potential adverse effects of FFP include transmission of blood-borne infections, febrile or allergic reactions, and transfusion-related acute lung injury.

Plasma exchange

Plasma exchange may be required to correct the coagulopathy or control refractory bleeding in patients at risk for volume overload with FFP alone. However the efficacy of plasma exchange in ESLD has not been demonstrated in controlled trials. Plasma exchange is used primarily to prepare patients for liver transplantation, or to manage patients with fulminant hepatic failure [118,119].

Other replacement therapy

Cryoprecipitate is a fraction of plasma rich in fibrinogen, FVIII, vWF and factor XIII. Cryoprecipitate may be required in patients with a severe co-

agulopathy and hypofibrinogenemia (< 100 mg/dL). Prothrombin-complex concentrates contain the vitamin K dependent clotting factors (FII, FVII, FIX and FX) in high concentration. Despite several reports of the safe use of these products, they should be avoided in patients with ESLD due to the risk of thrombotic complications [120,121].

Recombinant factor VIIa

Recombinant FVIIa (rFVIIa), is a synthetic analog of the naturally occurring serine protease enzyme, genetically engineered in baby hamster cells. In normal physiologic concentrations, FVIIa is enzymatically active only after binding tissue factor exposed at vascular injury sites. The tissue factor-FVIIa complex activates factors IX and X, ultimately accelerating thrombin generation. In high (pharmacologic) concentrations, FVIIa activates FX directly on the surface of activated platelets, independent of tissue factor [122]. The requirement for tissue factor or activated platelets localizes rFVIIa's procoagulant activity to the vascular injury site, thereby minimizing the risk of thrombotic complications.

Recombinant FVIIa is FDA approved for the treatment of bleeding in hemophilia patients with inhibitors. It has been used to correct the coagulopathy of ESLD, although limited data support its use in this setting. Multiple studies demonstrated prompt normalization of the PT in the majority of patients with baseline prolonged values, including those refractory to plasma infusions [11,102,123–128]. Higher doses achieve greater and more prolonged correction of the PT, suggesting a "dose-response" effect [11,124]. However, the effect is transient, even at higher doses, reflecting rFVIIa's short half-life of approximately 2 hours.

The prompt predictable correction of the PT, provides a rationale for the prophylactic and therapeutic use of rFVIIa. However, the current evidence supporting its use in ESLD is limited to case reports and case series. Recombinant FVIIa was reported to prevent bleeding at the time of liver biopsy, intracranial pressure (ICP) monitor placement, pericardiocentesis, pancreatic aspiration, injection of hepatocellular carcinoma and colon polypectomy, and to reduce blood loss during orthotopic liver transplantation [123,124,126,129–131]. Prophylactic doses ranged from 5 to 120 μg/kg, with some patients receiving additional doses during or after the procedure [124,126].

Recombinant FVIIa also controlled refractory epistaxis, bleeding after dental extractions, hematuria, oozing from catheter sites, and gastrointestinal bleeding in a small number of patients with ESLD [125,132,133]. A single dose (50–110 μg/kg) achieved hemostasis in cirrhotic patients with variceal hemorrhage refractory to standard measures. However, early rebleeding occurred in 25% of cases, and there was a high mortality rate from bleeding-related causes [102,134]. In another study, the majority of patients with persistent uncontrolled bleeding after rFVIIa, had a complex coagulopathy due to liver disease, which suggested uncertain efficacy in this particular population [135].

Despite rFVIIa's excellent overall safety record in hemophilia patients, its safety in patients with other thrombotic risk factors is not established. Reports of increased levels of several coagulation activation markers, especially after higher doses, fuel a theoretical concern that a rFVIIa-induced "thrombin burst" could exacerbate subclinical DIC [11,124,136]. However, none of the reported patients developed clinical DIC, and no adverse effects occurred in the majority of other studies [11,124]. There are a few anecdotal reports of DIC and thrombosis in patients with ESLD receiving rFVIIa, although a causal connection to rFVIIa was not confirmed [124,131].

Recombinant FVIIa has several advantages over plasma in ESLD, including more rapid and predictable correction of the PT, a lower infection risk, and effectiveness in small volumes [125,126]. However, transient shortening of the PT does not guarantee hemostasis. Moreover, because of rFVIIa's short half-life, effective hemostasis may be followed by recurrent bleeding in the absence of definitive therapy [102,133]. The optimal dose and dosing schedule for prophylaxis or treatment of bleeding are unknown, and may depend on the severity of the coagulopathy and clinical indication. It is also unclear to what extent the hemostatic effect of rFVIIa depends on the platelet count and other clotting factor levels. Larger prospective controlled trials are required to confirm efficacy and safety in ESLD and to define guidelines for its cost-effective use.

Thrombocytopenia

Platelet transfusions are indicated in actively bleeding patients with platelet counts <50,000–75,000. Since platelets are suspended in plasma, a single apheresis product provides a unit of plasma, also replacing clotting factors. However, the plasma in platelets has a lower concentration of FV and FVIII than FFP. Prophylactic platelet transfusions are often administered before invasive procedures in patients with platelet counts < 50,000. Since thrombocytopenia is typically mild in ESLD, they are rarely required in stable patients who do not require invasive procedures. A platelet count of 10,000 is a common trigger for prophylactic platelet transfusions in stable thrombocytopenic patients. A higher threshold may be appropriate for patients with other hemostatic defects or risk factors for bleeding. Post-transfusion platelet counts are used to assess recovery and guide subsequent therapy. The platelet count increment will be blunted in patients with splenomegaly because of sequestration of transfused platelets [38,39]. Other causes of platelet refractoriness include DIC, infection, and alloimmunization caused by platelet-specific and /or HLA antibodies. The potential benefits of platelet transfusions must be weighed against the risk of alloimmunization, an important consideration for patients awaiting liver transplantation. The use of leukoreduced products will reduce the risk of alloimmunization. Corticosteroids and IVIG are occasionally effective in patients with a clinical presentation suggesting ITP [72,74,75]. The clinical use of recombinant

thrombopoietin is still investigational, and trials in patients with liver disease have not yet been performed.

Platelet dysfunction

The indications for specific therapy to improve platelet function are unclear. Since severe anemia may also impair platelet function, red cell transfusions should be considered for patients with hematocrits < 30% [80]. Desmopression (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic analog of antidiuretic hormone which stimulates the release of vWF from endothelial cells. DDAVP significantly shortens bleeding times in up to 60% of patients with cirrhosis [137–140]. The effect is transient, with maximal shortening 30–60 minutes after a single dose, and does not depend on the platelet count [137]. Although the mechanism is still not well understood, DDAVP appears to increase platelet adhesiveness. There are no studies confirming its clinical efficacy for the prevention or treatment of bleeding in ESLD. Because of the complexity of the hemostatic derangement, a transient shortening of the bleeding time may not significantly reduce the risk of bleeding. DDAVP did not reduce intra-operative blood loss or improve control of active variceal hemorrhage in two randomized trials [141,142]. However, a trial of DDAVP is reasonable in patients with refractory bleeding and a prolonged bleeding time or abnormal PFA.

Disseminated intravascular coagulation

Although laboratory evidence of low grade DIC is common in ESLD, specific therapy is rarely required. When DIC is suspected, therapeutic strategies should focus on detection and reversal of potential precipitating factors, such as infection. Replacement of clotting factors, coagulation inhibitors, and platelets may be necessary in patients with active bleeding, using laboratory tests to guide therapy. Anticoagulation with heparin is not recommended because of the unacceptably high risk of bleeding. Infusion of antithrombin concentrate normalized fibrinogen survival in cirrhotic patients, but had no significant effect on molecular markers of coagulation activation [97,143]. Currently, there is no evidence that antithrombin replacement prevents the clinical complications of DIC or improves outcome in ESLD.

Systemic fibrinolysis

Patients with mild systemic fibrinolysis who are not bleeding do not require specific therapy. In contrast, those with severe fibrinolysis and serious bleeding require replacement of hemostatic components. FFP replaces α_2-antiplasmin as well as clotting factors and cryoprecipitate contains fibrinogen and FVIII in high

concentration. Antifibrinolytic agents (epsilon aminocaproic acid, tranexamic acid) inhibit plasmin generation and may control diffuse bleeding [19,34,35]. However, because of the frequent simultaneous activation of coagulation, there is a high risk of thrombotic complications in this particular population. Antifibrinolytic agents may be considered in selected patients with fibrinolytic bleeding unresponsive to plasma and platelet transfusions after exclusion of DIC.

Invasive procedures

Patients with ESLD and coagulopathy are assumed to have an increased risk of bleeding with invasive procedures, although the magnitude of risk is not well defined. The bleeding risk is likely higher in patients with multiple hemostatic defects, renal failure, or a prior bleeding history [144,145].

Liver biopsy

Clinically significant bleeding is uncommon after percutaneous liver biopsy, complicating 0.35%–0.7% of cases [146–149]. Severe hemostatic defects are considered a contraindication to the procedure [150]. However, there is no consensus on acceptable hemostatic parameters, which vary considerably among practicing gastroenterologists and academic centers [151,152]. Peripheral blood coagulation tests correlate poorly with the severity of bleeding from the liver biopsy site observed at laparoscopy [146,153–155]. In most studies, a mildly prolonged PT (within 4 seconds of control) did not increase the risk of bleeding [146,153,155,156]. In contrast, a severe coagulopathy may predispose to procedure-related bleeding [147,149,157]. Mild thrombocytopenia (platelet count >50,000–100,000) does not appear to increase the risk of post-biopsy bleeding [146,153,158]. More severe thrombocytopenia (<50,000) was associated with bleeding complications in some [158] but not all studies [154,159]. A prolonged bleeding time (>12 minutes) was reported to confer a fivefold higher risk of post-biopsy bleeding [160]. However, the bleeding time is not a validated predictor of bleeding after invasive procedures, and most centers do not include it in their pre-biopsy testing [151].

The available data suggest that hemostasis screening tests do not reliably predict bleeding after liver biopsy. Various technical aspects of the procedure, including the number of punctures and underlying liver pathology, may also affect the risk of bleeding. Although there are no universally accepted guidelines, most authorities recommend a minimum platelet count of >50,000 to 80,000 and a PT within 3–4 seconds of control values [110,151,161–164].) FFP and platelet transfusions are recommended for a PT > 3 –4 seconds above control (INR >1.4), and a platelet count < 50,000–60,000, respectively, although there is no evidence that prophylactic therapy prevents bleeding complications [161,162,164]. Preliminary studies suggest rFVIIa provides effective prophylaxis, although there is insufficient data to support its routine use [124]. Alternative biopsy methods

(“plugged” percutaneous or transjugular biopsy) may be safer for patients with severe coagulation defects that cannot be corrected [154,157,163,165].

Intracranial pressure monitors

Patients with fulminant liver failure often undergo ICP monitor placement for detection of cerebral edema. Bleeding complications occur in 3%–18% of patients, depending on the particular monitoring technique [166]. Since there is no consensus on “safe” coagulation parameters for monitor placement, acceptable values are often defined by neurosurgical consultants. Plasma or platelets are frequently transfused to correct hemostatic defects before the procedure. However, the large volumes of plasma usually required have a theoretical risk of exacerbating cerebral edema. Recombinant FVIIa transiently corrects the PT, allowing ICP monitor placement, although the optimal dose and duration of therapy is unknown [126].

Central venous catheters

Placement of central venous catheters in hemostatically compromised patients with ESLD is associated with a low risk of bleeding, with major bleeding complications reported in 0%–0.2% of cases, and minor bleeding complications reported in 1%–12% of cases [144,167–170]. The infrequency of bleeding suggests that routine administration of blood products is unnecessary before catheter placement. Prompt application of pressure may prevent hematoma formation, even in patients with coagulation defects.

Paracentesis and thoracentesis

Excessive bleeding occurs in 0%–3% of patients undergoing paracentesis; 0% to 1.2% of procedures are complicated by major hemorrhage requiring transfusion [145,171–175]. One study found no significant difference in the incidence of bleeding between patients with and without hemostatic defects, or between those who did and did not receive prophylactic plasma infusions before the procedure [145]. In another large series of 1,100 paracenteses, there were no significant bleeding complications in cirrhotic patients with platelet counts $<50{,}000$ and/or INR values ≥ 1.5 [175]. Several consensus guidelines recommend against routine administration of blood products before paracentesis, suggesting coagulation defects are a contraindication only in patients with clinically overt fibrinolysis or DIC [173,176,177].

The limited available evidence suggests bleeding is uncommon after thoracentesis in patients with ESLD, even in the absence of prophylactic blood products [145]. However, the American Thoracic Society and the American College of Physicians identify a coagulopathy as a contraindication to

thoracentesis and pleural biopsy, recommending a minimum platelet count of 50,000 [178,179]. Because of difficulty detecting bleeding and risk of hemothorax, severe coagulation defects should be corrected.

Summary

Patients with ESLD develop multiple hemostatic defects, the severity of which depends on the degree of hepatic injury. In addition, other coexisting complications such as uremia and esophageal varices may predispose to abnormal bleeding. The hemostatic derangement of ESLD has a multifactorial etiology. Impaired hepatic synthesis of coagulation proteins and TPO is a major cause of coagulation defects, fibrinolyisis, and thrombocytopenia. However, the widely variable range of all hemostatic parameters suggests different mechanisms predominate in individual patients. Although the hemostatic derangement of ESLD usually results in a bleeding tendency, it occasionally predisposes to DIC or thrombosis.

Hemostasis laboratory testing is used to assess disease severity and bleeding risk, and to monitor the response to therapy. However, no particular coagulation profile reliably predicts bleeding. The INR is valid for reporting PT results within an institution, but does not standardize the PT in ESLD independent of the particular thromboplastin used. FFP, cryoprecipitate and platelet transfusions remain the mainstay of therapy for patients who are actively bleeding or require invasive procedures. Until larger controlled trials confirm efficacy and safety in ESLD, rFVIIa should be used with caution based on an individual risk/benefit assessment. There is no consensus on acceptable coagulation laboratory parameters for performance of invasive procedures. Nevertheless, most experts recommend correction of severe coagulation defects, especially before high-risk procedures, in locations where bleeding is difficult to control. Decisions about prophylaxis should be based on the type of procedure, severity of hemostatic defects, co-existing risk factors, and the patient's bleeding history.

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