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<p>The coagulation “cascade” model accurately represents the mechanisms of the prothrombin time and activated partial thromboplastin time tests. However, these tests and the “cascade” model do not accurately reflect the risk of hemorrhage or thrombosis in vivo. In hepatic insufficiency, a balanced reduction in the levels of most of pro- and anticoagulant proteins produced in the liver does not impair thrombin generation until levels are quite low. However, the ability of the coagulation system to tolerate or recover from an insult is markedly impaired in liver disease. This allows the coagulation system to be more easily tipped into a state favoring either hemorrhage or thrombosis.</p>	
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<p>Patients who have liver disease commonly present with alterations in platelet number and function. Recent data have questioned the contribution of these changes to bleeding complications in these patients. Modern tests of platelet function revealed compensatory mechanisms for the decreased platelet number and function, the most prominent compensatory mechanism being substantially elevated levels of the adhesive protein von Willebrand’s factor. Consequently, standard diagnostic tests of platelet functions seem to be of little use to predict bleeding complication in patients who have liver disease. This article outlines the role of platelet abnormalities and possibilities for platelet function testing in patients who have liver disease.</p>	
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<p>The incidence of hyperfibrinolysis in patients with cirrhosis is still debated. The reasons for this uncertainty probably lie in the lack of appropriate laboratory tests for its evaluation. There is a relative consensus, however, that hyperfibrinolysis can complicate the clinical course of liver cirrhosis, especially in cases of moderate to severe liver failure. Hyperfibrinolysis correlates positively with the severity of underlying liver disease, and low-grade systemic fibrinolysis is found in 30% to 46% of patients who have end-stage liver disease. Accelerated intravascular coagulation with secondary hyperfibrinolysis has been reported in patients who have liver failure. Hyperfibrinolysis may delay primary hemostasis, thereby aggravating variceal bleeding and facilitating recurrence.</p>	

Superimposed Coagulopathic Conditions in Cirrhosis: Infection and Endogenous Heparinoids, Renal Failure, and Endothelial Dysfunction 33

Jasper H. Smalberg and Frank W.G. Leebeek

In this article, the authors discuss three pathophysiologic mechanisms that influence the coagulation system in patients who have liver disease. First, bacterial infections may play an important role in the cause of variceal bleeding in patients who have liver cirrhosis, affecting coagulation through multiple pathways. One of the pathways through which this occurs is dependent on endogenous heparinoids, on which the authors focus in this article. Secondly, the authors discuss renal failure, a condition that is frequently encountered in patients who have liver cirrhosis. Finally, they review dysfunction of the endothelial system. The role of markers of endothelial function in cirrhotic patients, such as von Willebrand factor and endothelin-1, is discussed.

Heparin-like Effect in Liver Disease and Liver Transplantation 43

M. Senzolo, E. Cholongitas, U. Thalheimer, Anne Riddell, S. Agarwal, S. Mallett, C. Ferronato, and A.K. Burroughs

Liver cirrhosis is characterized by impairment of primary and secondary hemostasis but it is not clear how this impairment is related to the bleeding problems seen in cirrhosis. This delicate hemostatic balance can be perturbed by numerous conditions, such as variceal bleeding, renal failure, or infection/sepsis, which may lead to worsening of coagulation status to date. The role of endogenous heparinoids (glycosaminoglycans) in the coagulopathy of patients who have cirrhosis has been demonstrated by thromboelastography with the addition of heparinase I in patients who have recent variceal bleeding and infection. The heparin-like effect has also been demonstrated to be part of the coagulopathy seen after reperfusion in patients who have cirrhosis and are undergoing liver transplant. Therapeutic implications of these findings are not clear at the moment and the use of drugs able to cleave heparinoids should be explored.

Tests of Coagulation in Liver Disease 55

Armando Tripodi

The complex coagulation defect secondary to chronic liver disease is considered responsible for the bleeding problems that often are associated with the disease. Accordingly, clinicians order laboratory tests to assess the risk of bleeding and rely on these results to make decisions about the management of the associated coagulation disturbances. Recent data, however, indicate that the abnormality of coagulation in stable cirrhosis is more a myth than a reality and may help explain why the prolonged global coagulation tests are poor predictors of bleeding in this setting. Alternative tests more closely mimicking what occurs in vivo should be developed and investigated in appropriate clinical trials to determine their value in the management of bleeding in cirrhosis.

The International Normalized Ratio of Prothrombin Time in the Model for End-stage Liver Disease Score: A Reliable Measure 63

Patrick S. Kamath and W. Ray Kim

The Model for End-stage Liver Disease (MELD) has been demonstrated to be an excellent predictor of survival in patients who have end-stage liver disease. It is derived from the international normalized ratio (INR) of prothrombin time, serum creatinine, and serum total bilirubin. The major use of the MELD score is to prioritize allocation of organs for liver transplant among patients who have chronic liver disease. Virtually every study that has looked at the MELD score as a predictor of survival has demonstrated that the MELD score using the INR with international sensitivity index calibrated for patients on warfarin has a 'c' statistic of approximately 0.8, indicating excellent discrimination.

International Normalized Ratio of Prothrombin Time in the Model for End-stage Liver Disease Score: An Unreliable Measure 67

Russ Arjal and James F. Trotter

The current basis for deceased donor liver allocation is the Model for End-stage Liver Disease (MELD) score, which is an objective means of predicting 90-day patient survival. Although the MELD system is a vast improvement over the prior allocation scheme, published studies have refuted the United Network for Organ Sharing statement that "the MELD and PELD [Pediatric End-stage Liver Disease] formulas are simple, objective and verifiable and yield consistent results whenever the score is calculated." In particular, wide inter-laboratory variation exists in the most heavily weighted MELD determinant, the international normalized ratio (INR). Whether this variation impacts the equitable distribution of deceased donor livers is unclear. However, the current technique for measuring the INR has the potential to detract from the expressed purpose of MELD-based allocation, which is to prioritize liver transplant candidates across the country with parity, using an objective scoring system.

Blood Products, Volume Control, and Renal Support in the Coagulopathy of Liver Disease 73

Curtis K. Argo and Rasheed A. Balogun

Plasma-based products are commonly used in patients who have chronic liver disease to treat perceived coagulopathy despite unproven efficacy and potentially severe risks, such as transfusion-related acute lung injury, which carries a high mortality rate. Moreover, volume expansion may acutely worsen portal hypertension and increase bleeding from the collateral portal vascular bed. Although factor replacement therapy may be warranted in selected situations, its use should be restricted because of the limitations of target tests, such as international normalized ratio, which poorly reflects presence of bleeding diatheses in patients who have cirrhosis. Renal replacement therapies are frequent adjuncts in patients who have cirrhosis and are acutely decompensated, and may correct

uremia-related bleeding diathesis and assist in controlling vascular volume, although they are generally limited to use as a bridge to liver transplantation. Novel extracorporeal therapies are emerging and may also have significant interaction with the hemostatic system. Volume contraction and blood conservation therapies are relatively new and promising approaches to reduce use of blood products in liver transplantation.

The Role of Anti-Fibrinolytics, rFVIIa and Other Pro-Coagulants: Prophylactic Versus Rescue?

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Neeral L. Shah, Stephen H. Caldwell, and Carl L. Berg

Patients who have liver disease experience an increased risk for bleeding and resulting complications. Diseases affecting the liver can cause a deficiency of pro-coagulant factors or induce a state of increased clot breakdown. Although traditional tests of coagulation, such as prothrombin time or international normalized ratio (INR), may not accurately measure bleeding risk, many studies have assessed measures used to correct an increased INR and minimize adverse outcomes. This article discusses the use of activated factor VIIa and anti-fibrinolytic agents to treat coagulopathy in the setting of liver disease and the potential advantages and disadvantages of these alternatives, and the limitations of the current literature. This article also compares the limitations, risks, and potential benefits of prophylactic therapy to prevent bleeding before invasive procedures with rescue therapy for spontaneous and postprocedure bleeding, and describes the relative advantages and disadvantages of these two approaches.

Coagulopathy of Acute Liver Failure

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Santiago J. Munoz, R. Todd Stravitz, and Don A. Gabriel

Coagulopathy is an essential component of the acute liver failure (ALF) syndrome and reflects the central role of liver function in hemostasis. ALF is a syndrome characterized by the development of hepatic encephalopathy and coagulopathy within 24 weeks of the onset of acute liver disease. Coagulopathy in this setting is a useful prognostic tool in ALF and a dynamic indicator of the hepatic function. If severe, it can be associated with bleeding and is commonly a major obstacle to the performance of invasive procedures in patients with ALF. This review focuses on the epidemiology, pathophysiology, presentation, evaluation, and management of coagulopathy in ALF.

Hypercoagulation in Liver Disease

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Patrick G. Northup

The coagulopathy of liver disease is complex and often unpredictable. Despite clear evidence of an increased tendency for bleeding in patients who have cirrhosis, many circumstances also promote local and systemic hypercoagulable states. The consequences of hypercoagulability include the obvious morbidity and mortality of portal vein thrombosis, deep vein thrombosis, and pulmonary embolism, but possibly also include other end-organ syndromes, such as portopulmonary hypertension, hepatorenal syndrome, and spontaneous bacterial peritonitis. A more subtle contribution also could be responsible for progression of early fibrosis to

decompensated cirrhosis. Future research is needed to elucidate specific mechanistic pathways that might lead to local hypercoagulation and the clinical interventions that might prevent morbidity and mortality related to hypercoagulation in patients who have cirrhosis.

Parenchymal Extinction: Coagulation and Hepatic Fibrogenesis

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Quentin M. Anstee, Mark Wright, Robert Goldin, and Mark R. Thursz

Observations that hepatic inflammation and cirrhosis are associated with the presence of thrombi within the hepatic microvasculature and fibrin-fibrinogen deposition have led to epidemiologic studies showing that carriage of the factor V Leiden mutation, protein C deficiency, and increased expression of factor VIII are associated with rapid progression to cirrhosis in a chronic hepatitis C virus. Additional data suggest that this process may extend more broadly to progression in many forms of chronic liver disease. This article discusses the evidence for a role for coagulation cascade activity in hepatic fibrogenesis and explores the proposed pathogenic mechanisms including the downstream events of thrombin activation. Interference with either the generation of thrombin or its downstream activity may reduce hepatic fibrosis. Also examined are the implications for future therapeutic intervention.

Portal Vein Thrombosis and Budd–Chiari Syndrome

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Paulo Lisboa Bittencourt, Cláudia Alves Couto, and Daniel Dias Ribeiro

Venous thrombosis results from the convergence of vessel wall injury and/or venous stasis, known as local triggering factors, and the occurrence of acquired and/or inherited thrombophilia, also known as systemic prothrombotic risk factors. Portal vein thrombosis (PVT) and Budd–Chiari syndrome (BCS) are caused by thrombosis and/or obstruction of the extrahepatic portal veins and the hepatic venous outflow tract, respectively. Several divergent prothrombotic disorders may underlie these distinct forms of large vessel thrombosis. While cirrhotic PVT is relatively common, especially in advanced liver disease, noncirrhotic and nontumoral PVT is rare and BCS is of intermediate incidence. In this article, we review pathogenic mechanisms and current concepts of patient management.

Bleeding in Liver Surgery: Prevention and Treatment

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Edris M. Alkozai, Ton Lisman, and Robert J. Porte

Intraoperative blood loss and transfusion of blood products are negatively associated with postoperative outcome after liver surgery. Blood loss can be minimized by surgical methods, including vascular clamping techniques, the use of dissection devices, and the use of topical hemostatic agents. Preoperative correction of coagulation tests with blood products has not been shown to reduce intraoperative bleeding and it may, in fact, enhance the bleeding risk. Maintaining a low central venous pressure has been shown to be effective in reducing blood loss during partial liver

resections, and volume contraction rather than prophylactic transfusion blood products seems justified in patients undergoing major liver surgery. Although antifibrinolytic drugs have proved to be effective in reducing blood loss during liver transplantation, systemic hemostatic drugs are of limited value in reducing blood loss in patients undergoing partial liver resections.

Coagulation Disorders and Bleeding in Liver Disease: Future Directions**155**

Stephen H. Caldwell and Arun J. Sanyal

Much has changed since the characterization of the wide spectrum of abnormalities in the coagulation system in patients who have acute and chronic liver disease. With inherent limitations of conventional laboratory measures of coagulation in liver disease, it is now incumbent on us to explore how best to apply (or withhold) specific agents in specific situations. This will clearly require well focused translational research to understand and bring into sharp focus the various problems present, from dysfibrinogen to endogenous heparinoids, to uremia, to hyperfibrinolysis and even to unrecognized hypercoagulable conditions. The challenge lies ahead.

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