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Bleeding and Thrombosis in Patients With Cirrhosis: What's New?

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The liver is a central organ in the hemostatic system as it is the site of synthesis of many proteins involved in the activation and regulation of coagulation and fibrinolysis. In addition, the liver synthesizes thrombopoietin, which is a key hormone involved in the production of platelets. Patients with advanced chronic liver disease or acute liver failure develop alterations in their hemostatic system that are at least partly related to decreased synthetic capacity of the diseased liver. In addition, hemostatic changes in patients with liver disease may be related to systemic or intrahepatic activation of coagulation with consumption of hemostatic components. Finally, chronic endothelial cell activation resulting in elevated levels of endothelial-derived proteins such as von Willebrand factor contributes to the hemostatic changes associated with liver disease.

Although historically liver diseases were considered as bleeding disorders, nowadays it is recognized that liver diseases are not only associated with bleeding but also with thrombotic complications.[1,2] Because of the absence of high-quality clinical evidence, it is still unclear how to best prevent or treat bleeding and thrombosis in patients with liver diseases. The combination of laboratory studies with clinical observations, however, has led to a more rational approach to hemostatic management. In recent years, a number of international societies have issued clinical guidance documents in this area that share a number of concepts.[3–7] First, the concept of rebalanced hemostasis has become widely embraced.[8] The recognition that patients with liver disease have concomitant changes in both prohemostatic and antihemostatic systems leading to a relatively preserved hemostatic system has led to a much more restrictive approach to prophylactic correction of hemostasis with the aim to prevent bleeding, for example, before invasive procedures. It is now widely accepted that routine diagnostic tests of hemostasis, such as the platelet count and the prothrombin time, are unsuitable as indicators of hemostatic capacity in patients with cirrhosis.[9,10] As a consequence, routine prophylactic correction of a low platelet count and a prolonged prothrombin time by infusion of platelet concentrates or fresh frozen plasma is increasingly discouraged.[3–7] Second, the recognition of a hypercoagulable state in patients with cirrhosis, for example evidenced by enhanced in vitro thrombin generating capacity and an elevated risk for development of venous thromboembolism,[11,12] has led to increased awareness for the role of thromboprophylaxis, even in those patients with thrombocytopenia and/or prolonged prothrombin time.[3,7]

Here, the author outlines the recent developments in the prevention and management of bleeding and thrombosis in patients with liver disease.

HEMOSTATIC VERSUS NONHEMOSTATIC BLEEDING

Spontaneous and procedure-related bleeds have been feared complications of patients with liver disease. The most dramatic bleeding events have likely been witnessed during the early days of liver transplantation. A report from the 1980s on blood product use in >600 patients receiving a liver transplant in Pittsburg showed massive blood product use with red blood cell (RBC), fresh-frozen plasma (FFP), and platelet concentrate requirements of 29, 37, and 32 units per transplant on an average.[13] Interestingly, blood product use during liver transplantation has decreased substantially over time, and a 2015 report on >700 patients receiving a liver transplant in Quebec, Canada showed transfusion-free liver transplantation in the majority of patients with RBC, FFP, and platelet concentrate requirements of 0.5, 0.3, and 0.2 units per transplant on an average.[14] Spontaneous bleeds, notably upper gastrointestinal bleeds, complicate chronic liver disease until today. Such bleeds may still be dramatic and are associated with morbidity and mortality.[15]

Historically, bleeding complications in patients with cirrhosis were directly attributed to the hemostatic changes in these patients. The prolonged prothrombin time and a low platelet count were at that time interpreted as evidence for a profound hypercoagulable state. Nowadays, it is recognized that patients with cirrhosis are in a rebalanced hemostatic status, even in the presence of profound changes in the prothrombin time and platelet count. More importantly, it is now recognized that many bleeding complications in patients with cirrhosis are unrelated to hemostatic failure.[4] For example, variceal bleeding is related to portal hypertension with a negligible role for the hemostatic system. The observations that anticoagulant treatment is not associated with a high risk of variceal bleeding[16] and that the severity and outcome of variceal bleeding is similar in patients who were or were not using anticoagulant drugs at the time of the bleed[17] support the concept that variceal bleeding is independent of hemostatic dysfunction. Also bleeding during liver transplantation may in part be related to portal hypertension, and

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some centers perform preoperative phlebotomy with the aim to reduce pressure-related bleeding.[14] Bleeding may also be caused by mechanical injury. Such bleeds include inadvertent puncture or laceration of vessels during invasive procedures including liver transplantation. Finally, bleeds that are likely related to hemostatic failure may occur, including bruising, epistaxis, oozing from puncture wounds, and dental bleeds. Such bleeds are largely mild and rarely necessitate hemostatic therapy.

Recent clinical guidance documents advise against prophylactic administration of blood products to prevent spontaneous or procedure-related bleeding.[3,4,6,18] When bleeding occurs, clinicians are inclined to use prohemostatic treatment with blood products, factor concentrates, or antifibrinolytics. However, as many bleeds in patients with cirrhosis are unrelated to hemostatic failure, it has been argued that hemostatic treatment should not be used in the initial phases of treatment.[19] Rather, portal hypertension-related bleeds should be managed by pharmacological interventions that reduce portal pressure combined with local measures to stop the bleeds (eg, endoscopic interventions to treat a ruptured varix). Mechanical bleeds may be treated by local measures, for example, local pressure in case of a bleed following dental extraction or ligation of an injured vessel during (transplant) surgery. Recent studies in patients with variceal bleeding have shown that hemostatic treatment with, for example, fresh frozen plasma or tranexamic acid is ineffective and may do harm,[20,21] which supports a restrictive approach to hemostatic therapy in bleeding cirrhosis patients. Only in those patients with intractable bleeds or in patients with significant bleeding during transplant surgery, prohemostatic treatment is indicated. Low volume products such as fibrinogen concentrate and prothrombin complex concentrate may be preferred over fresh frozen plasma and platelet concentrate, as the latter may increase portal pressure and exacerbate portal hypertension-related bleeds.[22] Furthermore, large quantities of fresh frozen plasma are required to normalize coagulation parameters, and the yield of platelet concentrates may be low.[23]

In aggregate, the recognition that bleeding in patients with cirrhosis frequently is unrelated to hemostatic failure has led to a restrictive approach to prohemostatic therapy, both in prophylactic and in a treatment setting. Figure 1 summarizes the types of bleedings and potential therapeutic strategies.

BLEEDING RISK IN RELATION TO HEMOSTATIC CHANGES IN THE CRITICALLY ILL

The concept of rebalanced hemostasis has been developed using studies in patients with compensated cirrhosis or in stably decompensated patients.[24–26] Studies in patients with acute liver failure (without underlying chronic liver disease) suggested that rebalanced hemostasis also remains in these critically ill patients, which have profound hemostatic abnormalities.[27,28] Importantly, bleeding complications in patients with acute liver failure are rare. In a study of >1700 patients with acute liver failure, clinically significant bleeding occurred in only 11% of patients, despite a median international normalized ratio of 2.7 and platelet count of 96×10^9/L on admission.[29]

More recent studies have assessed hemostatic changes in critically ill patients with cirrhosis.[30–33] Also in these patients, there is laboratory evidence for rebalanced hemostasis, although there are notable hypercoagulable and hypocoagulable features in the

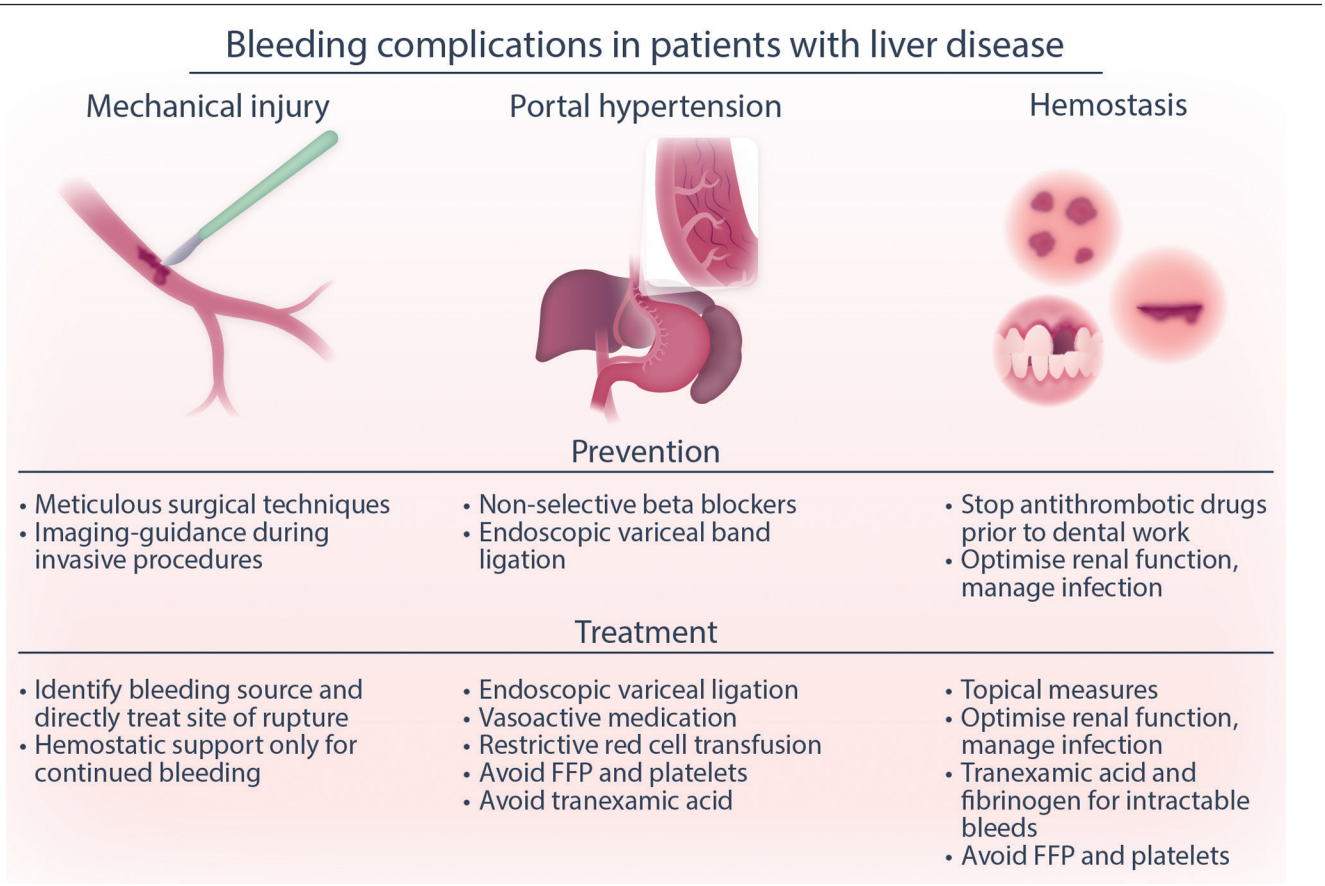

Figure 1. Categories of bleeding in liver disease. Bleeding in patients with liver disease may be due to mechanical injury (by inadvertent laceration of a vessel during surgery or a minor invasive procedure), portal hypertension-related causes (eg, variceal bleeding), or hemostatic failure (bleeding following dental extraction, bruising, and bleeding from puncture wounds). Shown are strategies to prevent and treat these different types of bleeding complications. FFP = fresh-frozen plasma.

hemostatic system of these patients.[32] The combination of both hypercoagulable and hypocoagulable features appears exaggerated in patients with additional complications including infection, renal failure, and progression from acute decompensation to acute-on-chronic liver failure.[34]

Bleeding risk in critically ill patients with cirrhosis is modest. In a study of >600 patients, bleeding occurred in 14%, and was mostly related to portal hypertension.[35] Indeed, hemostatic changes are not associated with bleeding risk in critically ill patients with cirrhosis. Rather, systemic inflammation was associated with bleeding risk. Similarly, bleeding in patients with acute liver failure was independent of hemostatic changes, but also seems related to inflammation.[27]

Although bleeding risk in critically ill cirrhosis patients appear independent of hemostatic changes, it has been proposed that decompensating events such as acute kidney injury, infection, and progression of disease are associated with hypocoagulable changes that contribute to bleeding.[34] There is some clinical evidence that acute kidney injury in patients with cirrhosis indeed is associated with an increase bleeding risk,[36] though the clinical evidence is based on a limited number of patients that bled. Although advanced hemostatic testing with viscoelastic whole blood tests or whole blood platelet function tests have been proposed to examine the hemostatic status of critically ill cirrhosis patients with decompensating events,[34] there is little evidence that prohemostatic interventions guided by such laboratory tests are useful in reducing bleeding risk. For now, it is important to recognize the limitations of hemostatic testing in predicting bleeding risk, and to understand that we do not have clear evidence that hemostatic therapy may be helpful. Additional study clearly is required to understand the best practices to prevent or treat bleeding in critically ill cirrhosis patients.

PORTAL VEIN THROMBOSIS

Although historically bleeding was the main concern in patients with cirrhosis, in recent years the focus has shifted toward thrombotic disease. Patients with cirrhosis not only experience bleeding complications, but are also at risk for deep vein thrombosis and pulmonary embolism, stroke, and myocardial infarction.[1] Prevention and treatment of these complications is complicated by the cirrhosis-associated hemostatic changes.[37] Next to these well-known thrombotic diseases, cirrhosis may be complicated by portal vein thrombosis (PVT), which is a rare disease in the general population, but occurs frequently in the sicker cirrhosis patients. Figure 2 outlines the recent insights in the pathogenesis and treatment of PVT that will be discussed below.

PVT is an unusual thrombotic disease, as it is frequently asymptomatic and recognized incidentally during routine imaging procedures. There are other notable differences between PVT and other venous thrombotic diseases. For example, the portal vein lacks venous valves, which are points of origin of deep vein thrombosis of the leg. In addition, whereas acquired or hereditary hypercoagulable states are recognized risk factors for deep vein thrombosis and pulmonary embolism, and there is accumulating evidence that hypercoagulability does not form a risk factor for PVT.[38–40] Rather, a reduction of flow in the portal vein, related to portal hypertension, appears to be the major risk factor for PVT.[38] In line with these observations, it has recently been shown that portal vein thrombi often do not contain classical thrombus components such as fibrin and platelets.[41] Rather, portal vein thrombi appear to consist principally from a pronounced thickening of the portal vein wall, notably the intima. Only in 30% of portal vein thrombi, a fibrin-rich structure was observed on top of the thickened intima. As intimal thickening

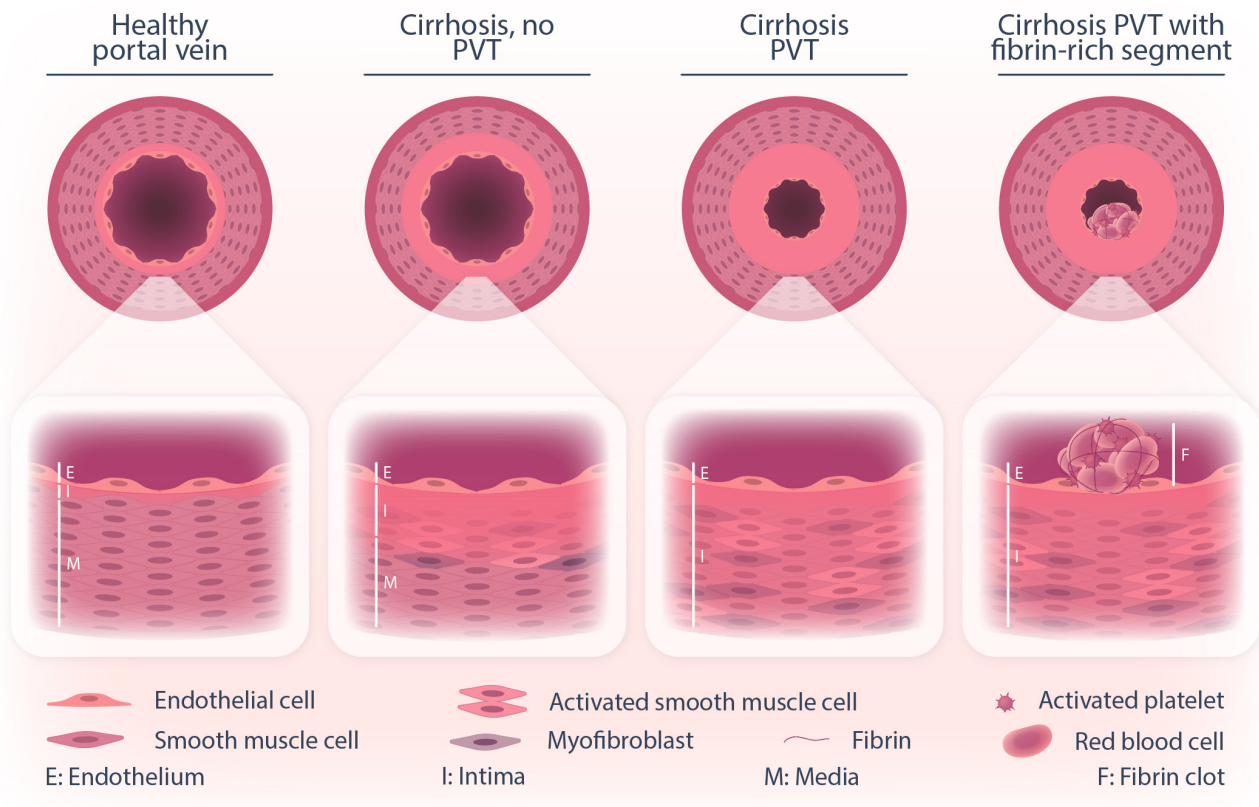

Figure 2. Pathogenesis of portal vein thrombosis. The portal vein wall develops intimal thickening in patients with cirrhosis, whereas no intima is present in a healthy portal vein wall. In patients with portal vein thrombosis, the intima thickening has progressed and may be accompanied by a fibrin-rich thrombus within the portal vein lumen. PVT = portal vein thrombosis.

of the portal vein also occurs in patients with cirrhosis without PVT, but not in healthy individuals, it is tempting to speculate that intimal thickening rather than thrombus formation is the initiating trigger of PVT development.

My group has, therefore, proposed that PVT may be a misnomer, and that portal vein stenosis or portal vein obstruction may be a better term for this complication in patients with cirrhosis.[41,42] Importantly, anticoagulant treatment frequently is not effective in dissolving a portal vein thrombus, reinforcing the notion that this may not be a classical thrombotic disease. In meta analyses, ~40% of portal vein thrombi recanalize without anticoagulation, whereas around 60%–70% recanalizes with anticoagulation.[43,44] Thus, although there is a definite effect of anticoagulation, the proportion of patients that benefit from anticoagulation is modest compared with the benefit of anticoagulation in the treatment of deep vein thrombosis and pulmonary embolism.

A recent individual patient data meta-analysis has demonstrated that anticoagulation in patients with cirrhotic nontumoral PVT provides a clear survival benefit in patients with cirrhosis.[43] Interestingly, this effect of anticoagulation was independent of PVT severity or recanalization, but was proportional to the duration of anticoagulant treatment. As previous studies have demonstrated that PVT per se does not increase mortality risk,[40] these data strongly suggest that anticoagulation has a PVT-independent effect on outcome. Thus, this study suggests that portal vein recanalization should not be considered as the goal of anticoagulant treatment in cirrhotic PVT. As anticoagulant therapy also is associated with a survival benefit in patients with cirrhosis without PVT,[45] anticoagulant therapy should perhaps be broadly considered with the aim of delaying decompensation and reducing mortality. The ongoing multicenter cirroxaban randomized trial (clinicaltrials.gov NCT02643212) is specifically testing the effects of anticoagulant treatment on the outcome of cirrhosis.

CONCLUSION

The combination of clinical and fundamental studies has tremendously increased our understanding of the complex hemostatic changes in patients with cirrhosis, and have led to a more rational approach to the prevention or treatment of both bleeding and thrombotic complications. Ongoing work will further refine the current clinical guidance documents, which hopefully will improve the quality of life and outcome of patients with liver diseases.

AUTHOR CONTRIBUTIONS

TL conceived of and wrote the manuscript.

DISCLOSURES

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