REVIEW ARTICLE

MECHANISMS OF DISEASE

The Coagulopathy of Chronic Liver Disease

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Chronic liver disease, particularly in the end stage, is characterized by clinical bleeding and decreased levels of most procoagulant factors, with the notable exceptions of factor VIII and von Willebrand factor, which are elevated.[1] Decreased levels of the procoagulants are, however, accompanied by decreases in levels of such naturally occurring anticoagulants as antithrombin and protein C.[1] In physiologic conditions, the coagulation system is balanced by these two opposing drivers (Fig. 1), but the mechanistic significance of the parallel decrease of both procoagulants and anticoagulants in patients with chronic liver disease escaped attention for many years. As a consequence, chronic liver disease is still considered the epitome of acquired bleeding disorders and is featured as such in most hematology textbooks. The basic laboratory tests of coagulation (i.e., measurement of the prothrombin time and activated partial-thromboplastin time) have been used to assess the risk of bleeding.

However, their results are poorly correlated with the onset and duration of bleeding after liver biopsy or other potentially hemorrhagic procedures.[2-7] These test results are also poorly correlated with the occurrence of gastrointestinal bleeding, the prototype of hemorrhagic events in patients with end-stage liver disease.[8,9] Additional evidence that argues against the clinical relevance of the coagulation defects as detected by conventional laboratory tests in determining the bleeding tendency in these patients can be drawn from the natural history of liver transplantation. In the past, this major surgical procedure required massive transfusions of plasma and other blood products to correct the marked abnormalities on tests of hemostasis (assessments of coagulation, platelets, and fibrinolysis) observed both preoperatively and perioperatively. The need for transfusions, however, has declined considerably over time — not because of any substantial change in medication, but rather because of improved surgical procedures.[10] Finally and most important, randomized clinical trials involving patients with chronic liver disease have shown that powerful procoagulant agents, such as recombinant activated factor VII, fail to control bleeding from the upper intestinal tract[11,12] or bleeding during liver transplantation,[13,14] even though the postinfusion prothrombin time is considerably shortened.[11] In this review, we consider the evidence regarding the balance in the hemostatic system (involving coagulation, platelets, and fibrinolysis).

THE HEMOSTATIC SYSTEM IN CHRONIC LIVER DISEASE

COAGULATION

The aforementioned observations question the validity of the prothrombin-time test and related tests for assessing the risk of hemorrhage and guiding the transfusion of fresh-frozen plasma or use of procoagulant agents in patients with chronic liver disease. An old dogma is being dispelled in favor of the newly emerging concept that

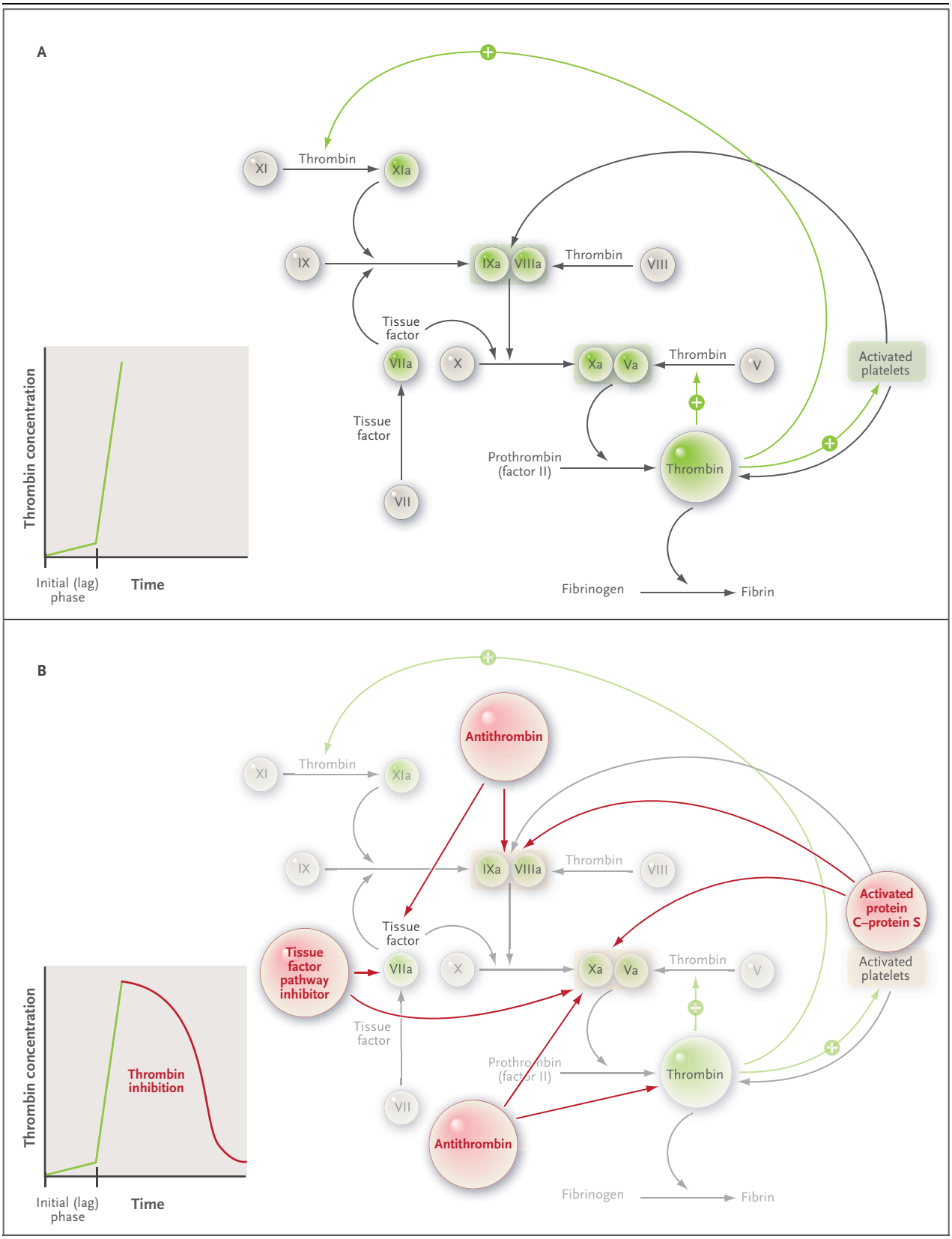

Figure 1 (facing page). Coagulation with Thrombin Generation and Inhibition.

Panel A shows thrombin generation, and Panel B shows thrombin inhibition. Examples of the in vitro curves for thrombin generation and inhibition are also shown. Procoagulant factors are represented by roman numerals; an "a" after the numeral indicates the activated form of the factor.

blood coagulation in such patients is rebalanced, owing to the parallel reduction of procoagulant and anticoagulant factors (Table 1). Indeed, studies show that plasma from patients with cirrhosis generates as much thrombin (the final enzyme of coagulation) as plasma from healthy subjects, provided that thrombin is measured by methods that reflect the action of both procoagulants and anticoagulants.[23,24] Thrombin generation in vivo and in vitro is down-regulated by thrombomodulin, a transmembrane protein situated on vascular endothelial cells that acts as the main physiologic activator of protein C (Fig. 2).[25] Plasma and reagents that are used to measure the prothrombin time do not contain thrombomodulin. Accordingly, this test measures the amount of thrombin generated in plasma as a function of the procoagulant drivers, but not the thrombin inhibited by the anticoagulant drivers, especially protein C, which is not fully activated in the absence of thrombomodulin. This might explain why the prothrombin-time test and related tests do not truly represent the balance of coagulation in vivo and are inadequate for assessing the risk of hemorrhage in those acquired conditions, such as the coagulopathies of liver disease and neonatal coagulopathies, in which there is a restored balance due to the concomitant decrease of procoagulants and anticoagulants.[26]

As for end-stage liver disease, another problem is that the prothrombin time expressed as the international normalized ratio (INR) is widely used as a prognostic index to calculate the patient's Model for End-Stage Liver Disease (MELD) score, which is used to prioritize candidates for liver transplantation. However, the INR was devised and validated to standardize across laboratories the prothrombin times in patients receiving anticoagulation therapy with vitamin K antagonists such as warfarin and its congeners. The INR cannot be used for patients with chronic liver disease unless an alternative system of standardization specifically developed for them is adopted.[27] This alternative system involves using a different calibration based on plasma from patients with chronic liver disease rather than plasma from patients receiving vitamin K antagonists.

Together, the above observations indicate that the bleeding tendency frequently observed in patients with end-stage liver disease should be explained by mechanisms other than hypocoagulability, such as those triggered by underlying conditions that favor hemorrhage (i.e., hemodynamic alterations subsequent to portal hypertension, endothelial dysfunction, bacterial infections, and renal failure[20,28-31]) (Table 2). It should also be understood that although rebalanced, the coagulation system in patients with chronic liver disease is not as stable as that in healthy persons, who have an excess of both procoagulants and anticoagulants. Therefore, the relative deficiency of both coagulation-system drivers makes the balance fragile in patients with liver disease and may tip it toward hemorrhage or thrombosis, depending on the prevailing circumstantial risk factors (Fig. 2C).

PLATELETS

Under normal conditions, platelets have a dual function. They adhere to damaged vessel walls through an interaction with the multimeric adhesive protein von Willebrand factor, thus promoting aggregation and ultimately the formation of the primary hemostatic plug. Platelets also support thrombin generation by assembling activated coagulation factors on their surfaces. Thrombocytopenia, a typical feature of chronic liver disease,[17] may therefore be another cause of bleeding (Table 1). However, very high levels of von Willebrand factor, a common finding in patients with chronic liver disease, may restore platelet adhesion to the subendothelium at sites of vascular injury (Table 1), as shown by in vitro experiments carried out under flow conditions mimicking those that occur in vivo.[15] Levels of ADAMTS 13, a naturally occurring plasma metalloprotease that limits in vivo the functions of von Willebrand factor on platelets, are reduced in patients with cirrhosis[16]; this may further contribute to the restoration of platelet function (Table 1). Finally, a platelet count as low as 60×10^9 per liter in platelet-rich plasma from patients with cirrhosis is usually sufficient to preserve thrombin generation at a level equivalent to the lower limit of the normal range in healthy subjects.[24]

Table 1. Patterns of Prohemostatic and Antihemostatic Drivers in the Different Phases of Hemostasis in Patients with Chronic Liver Disease.*

Hemostasis Phase	Prohemostatic Drivers	Antihemostatic Drivers
Primary hemostasis (platelet–vessel wall interactions)	High von Willebrand factor,[15] low ADAMTS 13[16]	Low platelet count[17]
Blood coagulation (thrombin generation and inhibition)	Low anticoagulant factors[1,18,19]: antithrombin, protein C High procoagulant factors: factor VIII[18,19]	Low procoagulant factors[1,18,19]: fibrinogen, factors II, V, VII, IX, X, XI
Fibrinolysis (clot dissolution)	Low plasminogen,[20] high PAI[20]	High t-PA,[20] low TAFI,[21,22] low plasmin inhibitor[20]

* ADAMTS 13 denotes disintegrin and metalloprotease with thrombospondin type 1 motif 13, PAI plasminogen activator inhibitor, TAFI thrombin-activatable fibrinolysis inhibitor, and t-PA tissue plasminogen activator.

FIBRINOLYSIS

Fibrinolysis is a highly regulated mechanism that, on deposition of fibrin within the vascular system, converts the proenzyme plasminogen into the active enzyme plasmin, which in turn degrades fibrin (Fig. 3). Under normal conditions, plasminogen-to-plasmin conversion is regulated by such activators as tissue plasminogen activator (t-PA), urokinase plasminogen activator, and activated factor XII. These activators (profibrinolytic drivers) are opposed by such antiactivators as t-PA inhibitors (mainly, plasminogen activator inhibitor [PAI]), plasmin inhibitor, and thrombin-activatable fibrinolysis inhibitor (TAFI), which cumulatively act as antifibrinolytic drivers. Any perturbation of this balance may result in hyperfibrinolysis, which increases the risk of hemorrhage, or hypofibrinolysis, which increases the risk of thrombosis.

Plasma hyperfibrinolysis has been reported in patients with chronic liver disease, but its mechanistic role in bleeding is still debated.[20] Uncertainty rests mainly on the lack of appropriate laboratory tests for its evaluation, because most observations are based on the measurement of the individual components of the system rather than on the overall activity stemming from the action of both profibrinolytic and antifibrinolytic drivers. Cirrhosis has been variably associated with laboratory changes favoring hyperfibrinolysis, such as increased levels of t-PA and reduced levels of plasmin inhibitor and TAFI, but also with changes favoring hypofibrinolysis, such as reduced levels of plasminogen and increased levels of PAI (Table 1). Hence, although contrasting results have been reported, the balance of fibrinolysis is probably restored in patients with liver disease by the parallel changes in profibrinolytic and antifibrinolytic drivers.[21,22]

PROCOAGULANT IMBALANCE IN CHRONIC LIVER DISEASE

GENERAL FEATURES

Overall, the aforementioned observations suggest that patients with chronic liver disease are not naturally "autoanticoagulated," as previously believed. This concept is reinforced by clinical evidence indicating that they are not protected from[32,33] and may even be at increased risk for[34] thrombosis, particularly but not exclusively in the portal venous system,[35,36] and especially in the presence of inherited prothrombotic mutations.[37]

Laboratory signs of a procoagulant imbalance, which was not evident in the previous studies,[23,24] have been reported in association with chronic liver disease.[18,19] As noted above, thrombin generation in vivo and in vitro is down-regulated by thrombomodulin (Fig. 2),[25] which effectively quenches thrombin generation when added to plasma from healthy subjects but is much less effective when added to plasma from patients with chronic liver disease.[18] This indicates that in such patients, the plasma is partially resistant to anticoagulation mediated by thrombomodulin. This resistance is evident only when the results of thrombin-generation tests are expressed as the ratio of thrombin activity in the presence of thrombomodulin to thrombin activity in its absence. The resistance is probably the result of two alterations typically found in patients with chronic liver disease[18,19]: markedly increased plasma levels of factor VIII (one of the most potent drivers of thrombin generation[38]) and the concomitant decrease in levels of protein C (one of the most potent anticoagulant drivers in quenching thrombin generation[25]). Although protein C is reduced owing to the impaired synthetic capacity of the

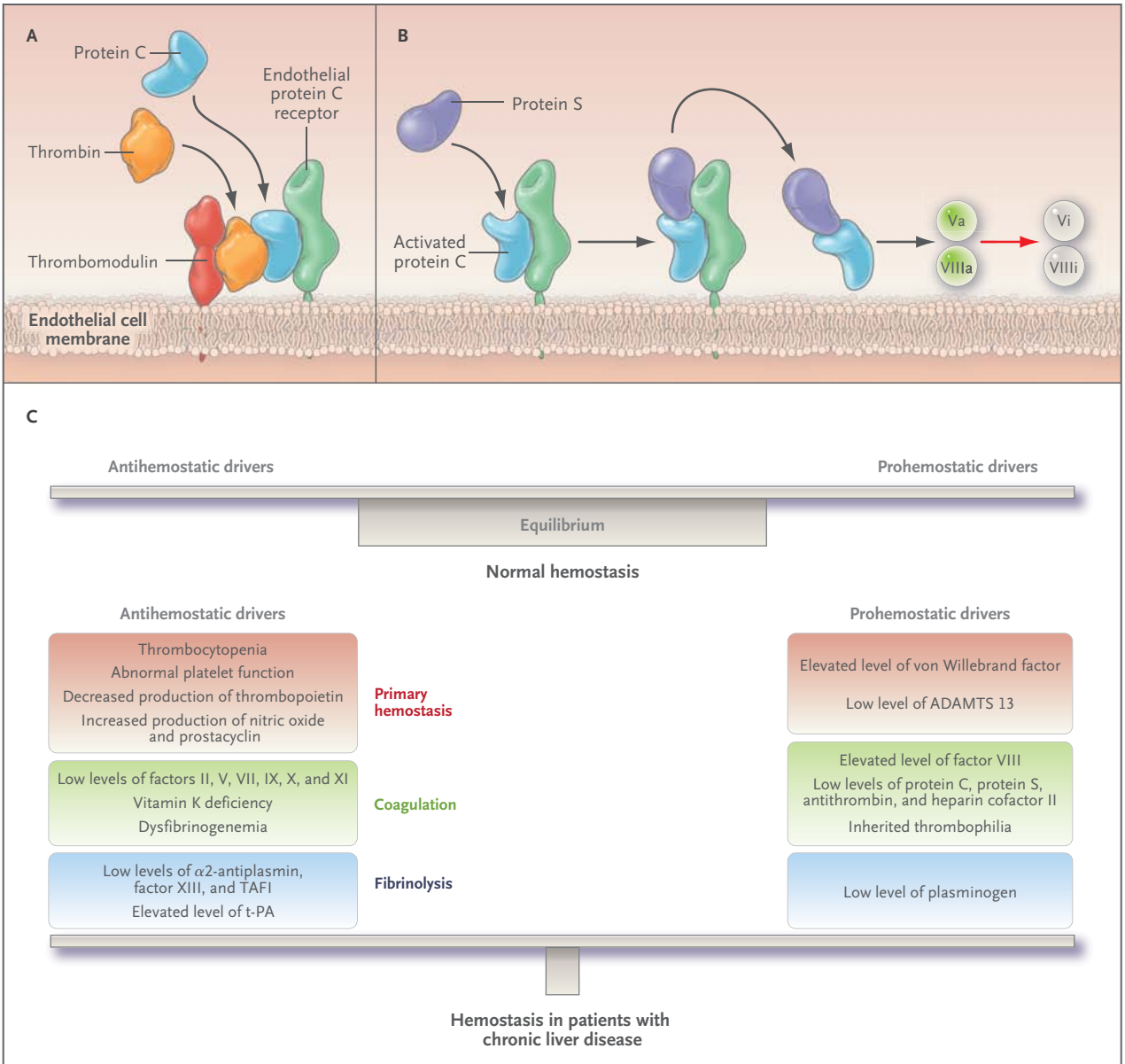

Figure 2. Protein C Activation by Thrombin on the Membrane of Endothelial Cells, and the Balance of Antihemostatic and Prohemostatic Drivers in the Different Phases of Hemostasis.

Thrombin and plasma protein C bind to the respective endothelial receptors, thrombomodulin and the endothelial protein C receptor (Panel A). On binding, protein C is quickly activated by thrombin (Panel B). Activated protein C forms a complex with its plasma cofactor, protein S, and eventually inhibits the activated forms of factor VIII (VIIIa) and factor V (Va), thus quenching thrombin generation. Plasma and reagents that are used to perform the prothrombin-time test (the laboratory test most widely used until now to assess the risk of hemorrhage in patients with chronic liver disease) do not contain sufficient amounts of thrombomodulin. Accordingly, the test is responsive to the amount of thrombin generated as a function of the procoagulants, but not to the thrombin inhibited by the anticoagulants. Therefore, the prothrombin time does not represent the balance of coagulation as it occurs in vivo. This might explain why the prothrombin-time test and related tests are not effective in assessing the risk of hemorrhage in patients with acquired coagulopathies (e.g., chronic liver disease) in which there is a concomitant decrease of procoagulants and anticoagulants. Panel C shows the balance of antihemostatic and prohemostatic drivers in the different phases of hemostasis in patients with chronic liver disease. ADAMTS 13 denotes disintegrin and metalloprotease with thrombospondin type 1 motif 13, TAFI thrombin-activatable fibrinolysis inhibitor, and t-PA tissue plasminogen activator.

Table 2. Underlying Conditions That Explain the Bleeding Tendency in Patients with Decompensated Chronic Liver Disease.

Hemodynamic alterations owing to portal hypertension[20,28,29]
Endothelial dysfunction[20]
Development of endogenous heparin-like substances owing to bacterial infections[20,29,30]
Renal failure[20,31]

liver, the increased levels of factor VIII are likely to be explained by decreased clearance of this moiety from plasma,[39] mediated by two mechanisms, one involving von Willebrand factor, and the other the low-density lipoprotein receptor–related protein.[39] Von Willebrand factor binds factor VIII in vivo and protects it from cleavage by plasma proteases and from premature clearance.[40] High plasma levels of von Willebrand factor in patients with cirrhosis[15] may be mechanistically involved in maintaining high plasma levels of factor VIII through the stabilization of its procoagulant activity. The low-density lipoprotein receptor–related protein, a multifunctional ligand that mediates the cellular uptake and subsequent degradation of factor VIII,[41] is inadequately expressed in patients with cirrhosis[39] and, in conjunction with high levels of von Willebrand factor, may help sustain the high plasma levels of factor VIII.

LABORATORY DETECTION

The procoagulant imbalance associated with chronic liver disease can be detected by measuring thrombin generation in plasma in the presence and absence of thrombomodulin.[18] An alternative method uses a snake-venom extract (Protac, Pentapharm)[19] that acts as a surrogate activator of protein C in a manner similar to that of thrombomodulin. Whereas the results of the first test are expressed as the ratio of the thrombin concentration generated in the presence of thrombomodulin to the concentration generated in its absence,[18] the results of the second test are expressed as the percentage of extract-induced coagulation inhibition, measured as the amount of thrombin generated in the presence versus the absence of the venom extract.[19] By definition, the higher the ratio or the lower the percentage of extract-induced coagulation inhibition, the greater the degree of procoagulant imbalance. As detected by these assays in the context of chronic liver disease, the procoagulant imbalance is negatively correlated with levels of plasma protein C and positively correlated with levels of factor VIII.[18,19] Furthermore, the degree of imbalance increases with the severity of cirrhosis as assessed by the Child–Pugh score.[18,19] Whether the procoagulant imbalance detected in the laboratory as thrombomodulin resistance is a risk factor for thrombosis in patients with chronic liver disease remains to be established by prospective studies. It must be recognized that although thrombin-generation tests mimic the conditions operating in vivo much more closely than do conventional tests, they remain artificial because they use platelet-free plasma and the amount of thrombomodulin added in vitro is chosen arbitrarily, not on the basis of the density of the protein on endothelial cells.

POSSIBLE CLINICAL IMPLICATIONS OF PROCOAGULANT IMBALANCE

The in vitro procoagulant imbalance associated with chronic liver disease[18,19] may have clinical implications. First, it calls into question the unrestricted use of plasma infusion to correct the results of conventional coagulation tests in patients undergoing invasive procedures. This is still a common practice, despite a lack of evidence from controlled, randomized trials and the recent guidelines of the American Association for the Study of Liver Diseases, which warn against the indiscriminate use of plasma therapy before liver biopsy.[42] Second, the procoagulant imbalance[18,19] may help explain mechanistically why these patients are not protected from clinical events such as peripheral-vein thrombosis, portal-vein thrombosis, atherothrombosis, and the progression of liver fibrosis. In the next sections, these potential clinical implications are discussed.

PERIPHERAL-VEIN THROMBOSIS

Retrospective studies showed that patients with chronic liver disease are not protected from venous thromboembolism (deep-vein thrombosis and pulmonary embolism).[32,33] Recently, a nationwide, population-based case–control study[34] involving 99,444 patients with venous thromboembolism and 496,872 controls showed that patients with liver disease had an increased relative risk of venous thromboembolism, with the risk being greater for deep-vein thrombosis than for pulmonary embolism and for cirrhosis than for noncirrhosis liver

disease. However, other studies have shown a low prevalence of venous thromboembolism among patients with chronic liver disease.[43,44] The retrospective design of all these studies makes it difficult to assess the true risk of venous thromboembolism among such patients. It is clear, however, that patients with chronic liver disease are not autoanticoagulated and may eventually have clinical manifestations of thromboembolism, even though the abnormal results of conventional coagulation tests would suggest the opposite.

Thrombosis in patients with chronic liver disease might become an emerging issue owing to their increasing life expectancy and changing lifestyle, which expose them much more than in the past to such circumstantial risk factors as tumors, surgery, obesity, prolonged hospitalization, and inadequate physical activity. Thus, the logical consequence is that patients with chronic liver disease who have peripheral-vein thrombosis should be treated with anticoagulants just as any other patient would; it is important to note that the long-term safety of this approach has not been studied. Furthermore, the in vitro procoagulant imbalance associated with chronic liver disease, confirmed by many independent studies,[45-47] suggests that these patients are eligible for antithrombotic prophylaxis when exposed to such risky situations as major surgery and prolonged immobilization. This notion contradicts current clinical practice, whereby patients with cirrhosis often receive no or suboptimal prophylaxis because of the perceived risk of bleeding.[48] Clinical studies are needed to determine the appropriate care of these patients.

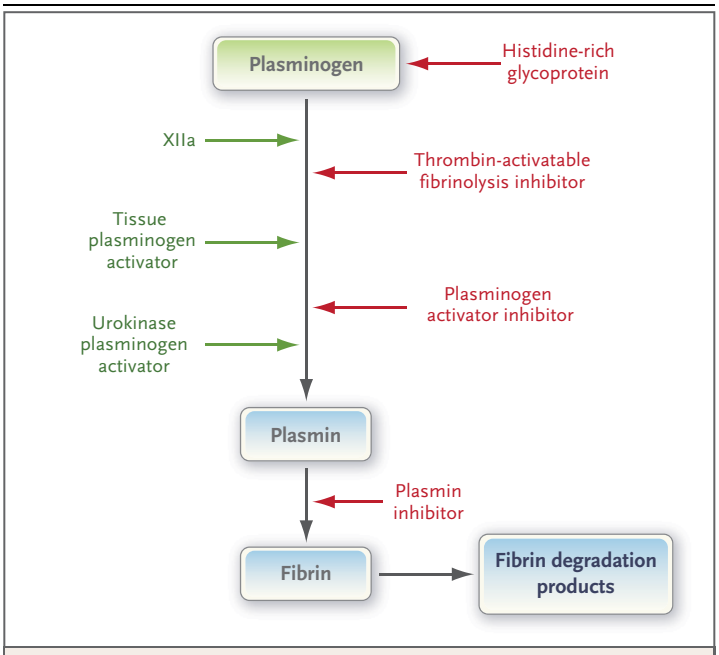

Figure 3. Fibrinolysis Activation and Inhibition.
Green and red arrows represent activators and antiactivators, respectively. XIIa denotes activated factor XII.

ARTERIAL THROMBOSIS

Even though it is not firmly established that patients with chronic liver disease have an increased risk of arterial thrombosis (i.e., coronary artery disease and stroke), they are not free from these and other clinical manifestations of atherothrombosis.[49] Furthermore, the occurrence of hepatic-artery occlusion after liver transplantation worsens the prognosis for these patients. Therefore, early detection of this complication is important.[50] Whether aspirin or other antiplatelet agents are indicated in the primary prophylaxis of this complication warrants evaluation in clinical trials.

PORTAL-VEIN THROMBOSIS

The prevalence of portal-vein thrombosis in patients with cirrhosis increases with the severity of the disease: approximately 1% among patients with compensated cirrhosis[35] but 8 to 25% among those who are candidates for liver transplantation.[36] Because not only reduced flow velocity[51] but also procoagulant imbalance and vessel-wall abnormalities (Virchow's triad)[52] are mechanistic factors in this complication, antithrombotic therapy (low-molecular-weight heparin or vitamin K antagonists) is commonly used.[53,54] This approach is relatively safe,[36] but varices may need to be treated (with vasoactive drugs or endoscopic ligation)[28] before patients start taking anticoagulants. Portal-vein thrombosis worsens the post-transplantation prognosis, so primary prevention with low-molecular-weight heparin or vitamin K antagonists should be considered in patients awaiting liver transplantation. Randomized clinical trials to test the efficacy of these drugs are under way.[55] However, because of the mechanistic role played by low levels of protein C in the balance of coagulation in patients with chronic liver disease,[18,19] vitamin K antagonists are perhaps not the ideal drugs. Protein C is a vitamin K–dependent protein, and treatment with vitamin K antagonists might therefore further reduce levels of this naturally occurring anticoagulant in patients with end-stage liver disease, increasing the risk of thrombosis.

The newer direct thrombin inhibitors and inhibitors of activated factor X[56] (e.g., dabigatran, rivaroxaban, and apixaban) may be attractive alternatives to vitamin K antagonists because they do not reduce protein C levels. Moreover, they do not require regular laboratory monitoring to adjust the dosage, whereas vitamin K antagonists require monitoring with the use of the INR, the validity of which has been questioned in patients with chronic liver disease.[57] Other potential advantages of these new drugs over low-molecular-weight heparin are their oral route of administration and their mechanism of action, which is independent of antithrombin (low in these patients). However, specially designed clinical trials are needed because patients with chronic liver disease are usually excluded from the randomized clinical trials of these drugs.[58-60]

LIVER FIBROSIS

Another consequence of procoagulant imbalance in chronic liver disease pertains to liver fibrosis and its progression. Two hypotheses are currently considered for the pathogenesis of this condition. Both involve coagulation, and they might be synergistic. One hypothesis centers on the role of microemboli. Obliterative lesions in the portal and hepatic veins frequently occur in patients with cirrhosis, owing to the formation of microthrombi that lead to tissue ischemia, cell death, and fibrosis through parenchymal extinction.[61]

Another hypothesis suggests that coagulation activation within the liver's vascular system may play a role in the development and progression of the fibrotic process. Thrombin, besides being a potent procoagulant, has many cellular effects that are mediated by a family of widely expressed G-protein–coupled receptors called protease-activated receptors (PARs).[62] Thrombin signaling through PARs expressed on hepatic stellate cells, which are responsible for tissue repair, might therefore play a crucial role in the mechanisms and progression of fibrosis.[63] The degree of thrombin-receptor expression is associated with the severity of liver disease, and it has also been observed that humans[64] and mice[65] with hypercoagulability due to a gain-of-function mutation in the factor V gene (factor V Leiden) have an accelerated progression of liver fibrosis. PAR1 antagonists can provide protection against experimental liver fibrosis in rodents,[63] and anticoagulant drugs slow fibrosis progression in mice.[65] Furthermore, low-molecular-weight heparin prevents hepatic fibrogenesis caused by the injection of carbon tetrachloride in rodents.[66] These observations are consistent with the hypothesis that thrombin generation and fibrosis are directly associated.[65] Accordingly, a controlled, randomized clinical trial is being carried out to investigate whether vitamin K antagonists can influence the progression of fibrosis in patients with hepatitis C (ClinicalTrials.gov number, NCT00180674).

CONCLUSIONS

Undoubtedly, patients with end-stage liver disease have prominent bleeding symptoms, particularly in the gastrointestinal tract. Yet evaluation of this bleeding tendency solely on the basis of abnormal levels of the conventional coagulation biomarkers should be reconsidered. When patients are assessed by means of global tests such as the thrombin-generation test, the results do not show hypocoagulability.[18,19,45-47] Thus, the main culprits for the bleeding tendency observed in patients with end-stage liver disease should be sought among underlying conditions that favor hemorrhage, such as portal hypertension, endothelial dysfunction, bacterial infection, and renal failure[20,28-31] (Table 2).

On the other hand, the restored balance of hemostasis afforded by the concomitant reduction of procoagulant and anticoagulant factors, together with increased levels of factor VIII (Table 1), might explain why patients with chronic liver disease are not protected from arterial and venous thrombosis. This apparent clinical paradox may be explained by the findings that these patients have a procoagulant imbalance in vitro owing to resistance to thrombomodulin[18,19,45-47] and that their thrombocytopenia is compensated for by increased plasma levels of the adhesive protein von Willebrand factor. Another dogma is being challenged by the finding that platelet activation plays a crucial role in the immune-mediated progression of liver disease in an animal model of viral hepatitis.[67]

In conclusion, the reassessment of hemostasis in patients with chronic liver disease challenges the dogma that the major coagulopathy in these patients leads consistently to bleeding. Other changes that accompany chronic liver disease may restore the balance of anticoagulant and procoagulant effects (Fig. 2C). In certain circumstances,

the risk of thrombotic events may be greater than the risk of hemorrhage. We speculate that drugs that are often regarded as contraindicated in patients with chronic liver disease may instead prove beneficial and should be tested in appropriate clinical trials.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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