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CHAPTER 13
Bleeding and thrombosis in cirrhosis

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Introduction to hemostasis

The hemostatic system is a crucial combination of protein cascades and cellular systems designed to maintain fluidity of blood under physiological circumstances and to quickly respond to vascular injury with the aim to limit blood loss and eventually restore vascular integrity [1]. The vasculature is lined with a continuous monolayer of endothelial cells, which actively suppress activation of the hemostatic system by both physical and biochemical mechanisms. In flowing blood, the red blood cells (RBCs), which constitute around 40% of the total blood volume are preferentially located in the center of the vessel, while actively pushing the much smaller blood platelets towards the vessel wall [2]. This process of platelet margination ensures that platelets constantly surveil the vessel wall for breaches. In an intact vasculature, platelets are maintained in a quiescent state by production of platelet inhibitors such as nitric oxide and prostacyclin by the endothelium. In addition, the endothelial glycocalix, a complex arrangement of sugar molecules attached to endothelial proteins and lipids, form a physical barrier between the blood and the endothelium [3]. The endothelium and the endothelial glycocalix also inhibit the coagulation system by promoting anticoagulant mechanisms, specifically the protein C system by endothelial thrombomodulin (TM), and antithrombin, whose anticoagulant action is enhanced by endothelial heparin-like molecules.

Platelets

When vascular integrity is disrupted, the hemostatic system is quickly activated to form a hemostatic plug consisting of platelets and fibrin [4]. The process of platelet plug formation is illustrated in Fig. 13.1. Upon exposure of collagen, the prime constituent of the extracellular matrix, to the bloodstream, platelet recruitment is initiated. First, von Willebrand factor (VWF), a large multimeric protein, attaches to the exposed collagen (Fig. 13.1A). Upon binding to collagen, VWF changes conformation and becomes able to interact with platelets, specifically via the platelet transmembrane receptor glycoprotein (GP) Ibα. The VWF–GP Ibα interaction is strong, but transient, and results in rolling of the platelet over the VWF surface, which slows down the platelet. VWF circulates in plasma in various multimeric sizes, with the largest multimers being the most reactive to platelets. The multimeric size of VWF is controlled by the protease ADAMTS13. ADAMTS13 is crucial as a deficiency of this protein results in the life-threatening disease thrombotic thrombocytopenic purpura (TTP), in which “ultra-large” VWF multimers result in spontaneous platelet aggregate formation in circulation in absence of vascular injury [5]. When the platelet has slowed down, it can permanently adhere to the extracellular matrix by interactions of two receptors (GPVI and α2β3) with collagen and by an interaction of αIIbβ3 with VWF (Fig. 13.1B).

Multiple processes including the interaction of collagen with its platelet receptors and generation of thrombin (FIIa) by the coagulation cascade activate the platelet, resulting in the release of platelet storage granules, and the synthesis of thromboxane A2 from arachidonic acid released from platelet membrane lipids (Fig. 13.1C). Release of ADP from platelet dense granules and synthesis of thromboxane A2 results in further platelet activation through the ADP receptor P2Y12 and the thromboxane receptor. A fully activated platelet becomes able to
interact with other platelets and form a three-dimensional aggregate (Fig. 13.1D). This process is accomplished via activation of αIIbβ3, which can bridge platelets by engaging with VWF or fibrinogen. Finally, activated platelets may express negatively charged phospholipids on their outer membrane. These negatively charged lipids are essential in supporting coagulation reactions [7].

Coagulation

The process of coagulation activation with subsequent fibrinolysis is summarized in Fig. 13.2. Coagulation is activated by exposure or activation of the transmembrane protein tissue factor (TF). Active TF is not exposed to the bloodstream under resting conditions, but vascular injury exposes TF on fibroblasts, smooth muscle cells, and possibly also on white blood cells to the vasculature. TF initiates the coagulation cascade, which consists of proteases and cofactors that circulate in inactive state in blood. The coagulation proteases activate each other leading to an enormous amplification of the coagulation signals.

Crucial coagulation reactions require a surface of negatively charged lipid, for example, provided by activated platelets, which ensures the activation of coagulation remains localized to the site of vascular injury. Coagulation culminates in the formation of thrombin (FIIa), which cleaves the soluble fibrinogen into fibrin which spontaneously polymerizes and forms the fibrin clot [8]. Thrombin also ensures stabilization of the fibrin clot through activation of factor XIII. FXIIIa crosslinks fibrin strands to each other to increase clot stability.

Although there appears to be redundancy in the coagulation system, all procoagulant proteins shown in Fig. 13.2 are required for hemostasis, as a deficiency in either of them is associated with a bleeding tendency. Generation of thrombin is regulated at three levels by natural anticoagulants tissue factor pathway inhibitor (TFPI), protein C, and antithrombin. TFPI and antithrombin can directly inhibit coagulation by direct interactions with TF-VIIa-Xa and thrombin (and other coagulation proteases), respectively. In contrast, protein C requires activation before it expresses anticoagulant activity. Protein C is activated by thrombin bound to the endothelial cell
receptor TM. When thrombin binds to TM, it loses its procoagulant capacity and turns into an anticoagulant by activating protein C. Activated protein C downregulates coagulation by inactivating the coagulation cofactors Va and VIIIa.

**Fibrinolysis**

When a hemostatic plug of platelets and fibrin has been generated to seal the damaged vessel wall, the endothelial layer is repaired after which the hemostatic plug can be removed. Removal of the hemostatic plug involves activation of the fibrinolytic system, which has a similar design as the coagulation system [9]. Release of tissue-type or urokinase plasminogen activator (tPA or uPA) into circulation results in the cleavage of plasminogen to plasmin. Plasmin cleaves fibrin into smaller soluble fibrin fragments which eventually lead to full clot removal. Similar to the coagulation system, the fibrinolytic system is tightly controlled by inhibitory systems, specifically plasminogen activator—inhbitior type 1 (PAI-1), which directly inhibits tPA and uPA, antiplasmin that directly inhibits plasmin, and thrombin activatable fibrinolysis inhibitor (TAFI) that delays plasminogen activation on the fibrin clot.

The liver is a central organ in the hemostatic system as it produces most of the proteins involved in hemostasis. It synthesizes thrombopoietin (TPO), the hormone involved in platelet production, all procoagulant- and anticoagulant-proteins with the exception of TFPI and factor VIII, and the fibrinolytic proteins plasminogen, TAFI, and antiplasmin.

**FIGURE 13.2** Processes resulting in the generation and subsequent breakdown of a fibrin clot. In this scheme, activatory processes are indicated by the uninterrupted lines, whereas regulatory or inhibitory steps are indicated by interrupted lines. After vessel wall damage, the transmembrane protein tissue factor (TF) is exposed to the bloodstream and binding of coagulation factor VII initiates a series of enzymatic reactions in which proenzymes are activated into active forms. This process results in the generation of thrombin (factor IIa), which cleaves fibrinogen into fibrin. Thrombin generation is regulated by tissue factor pathway inhibitor (TFPI) and antithrombin (AT), which inactivate factor VIIa and Xa, and thrombin, respectively. Furthermore, activated protein C, activated by a complex between thrombin and the endothelial cell receptor thrombomodulin (TM, inactivates cofactors Va and VIIIa. The fibrin clot can be broken down by the fibrinolytic system, a process initiated by release of tissue-type or urokinase plasminogen activator (tPA or uPA) from endothelial cells, macrophages, or renal epithelial cells. The plasminogen activators activate plasminogen to form plasmin, an enzyme capable of degrading fibrin into soluble fibrin degradation products. Plasmin generation is regulated by plasminogen activator—inhibitor type 1 (PAI-1), which is a direct inhibitor of tPA and uPA, and by plasmin inhibitor (PI), which inactivates plasmin. Furthermore, the fibrin clot is rendered more resistant to plasmin by activated FXIII and by activated thrombin activatable fibrinolysis inhibitor (TAFI), both of which are activated by thrombin generation in the coagulation cascade. Activated factor XIII crosslinks fibrin fibers to enhance the stability of the fibrin clot. Activated TAFI cleaves C-terminal lysine and arginine residues from partially degraded fibrin, and as these residues are binding sites for tPA and plasminogen required for fibrin-mediated plasminogen activation, fibrinolysis is slowed down as a result of removal of these amino acids. Source: Reprinted with permission from Karger Publishers (Basel, Switzerland). Lisman T, Leebeek FW. Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. Dig Surg 2007; 24: 250–258.

**Hemostatic changes in liver diseases**

As the majority of hemostatic proteins are synthesized in the liver, plasma levels of these proteins go down when the synthetic capacity of the liver becomes compromised [10,11]. Although plasma levels of hemostatic proteins appear to reduce proportional to the severity of disease, it is likely that decreased synthesis is not the only

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reason for decreased circulating levels of hepatocyte-derived proteins. As the liver is the site of clearance of hemostatic proteins, it is likely that circulating half-life of hemostatic proteins changes when liver disease progresses. In addition, levels of hemostatic proteins may decrease as a result of ongoing local or systemic activation of coagulation with consumption of hemostatic proteins. The hemostatic proteins not synthesized by the hepatocyte are primarily synthesized in the endothelium. As the endothelium in patients with liver diseases is generally in an activated state due to, for example, inflammation and alterations in blood flow, endothelial-derived proteins, notably VWF, FVIII, tPA, and PAI-1, are present in elevated levels [10–13].

Next to quantitative alterations in hemostatic proteins, qualitative changes also occur. The vitamin K-dependent coagulation factors may be altered in patients with vitamin K deficiency. Coagulation factors VII, IX, X, II, protein C, and protein S are modified after synthesis by a process involving vitamin K. Specifically, certain glutamic acid (glu) residues in the N-terminal part of these proteins are modified to a γ-carboxy glutamic acid (gla). This glu to gla modification increases the negative charge of these domains, and this negative charge is essential in the binding of the vitamin K-dependent proteins to a negatively charged phospholipid surface. Specifically, vitamin K-dependent proteins are bridged via their negatively charged gla domain to a negatively charged lipid surface through positively charged calcium ions. Although increased levels of incorrectly gla-modified coagulation factors are present in patients with liver diseases [14], this abnormality is mild and not substantially corrected by vitamin K supplementation [15,16].

A more profound effect has been demonstrated for the functional abnormalities in the fibrinogen molecule. Fibrinogen in patients with cirrhosis has been demonstrated to have a substantial excess of sialic acid residues, and it has been directly demonstrated that hypersialylated fibrinogen has a delayed fibrinogen to fibrin conversion [17–19]. Paradoxically, although cirrhotic fibrinogen has delayed clot formation, once the clot is formed it has prothrombotic properties which have been attributed to oxidation of the fibrinogen molecule [20].

Next to alterations in concentration or function of hemostatic proteins, liver diseases are characterized by a decreased platelet count. Thrombocytopenia of liver diseases is likely to be multifactorial and mechanisms involved include decreased platelet production by TPO deficiency and direct megakaryocyte toxicity and decreased platelet half-life possibly by autoantibodies, splenomegaly, and consumption [21]. Although it has long been thought that platelet function was also impaired in patients with liver diseases, modern studies have suggested platelet function to be intact or perhaps even enhanced in patients with liver diseases, and these studies have identified flaws in older studies [22]. Specifically, platelet function testing is unreliable in samples with a reduced platelet count. Having said that, most platelet function tests only capture part of all platelet functions. In addition, it is likely that in vivo the anemia of cirrhosis impairs platelet function given the role of RBCs in the process of platelet margination.

The hemostatic changes in patients with liver diseases are likely a result of a combination of decreased synthetic capacity of the diseased liver and an increased turnover of hemostatic factors by systemic or local activation of hemostasis leading to a consumptive coagulopathy (summarized in Fig. 13.3). Local activation of coagulation occurs within the diseased liver. Experimental animal models have demonstrated that liver injury results in decryption of TF, the natural activator of coagulation [23]. TF is normally not exposed to blood, and when it is, it usually assumes a confirmation that lacks procoagulant capacity (“encrypted TF” [24]). Hepatocytes express TF on their outer membrane, which in a healthy liver is fully encrypted. Following injury, decryption rapidly occurs with activation of coagulation and deposition of fibrin within the liver sinusoids and/or Space of Disse as a consequence.

In addition, the diseased liver may activate platelets, for example, by expression of collagens. Next to decreased synthesis and local or systemic consumption, patients with liver diseases have a reduced capacity to clear various hemostatic components including activated coagulation factors, activator–inhibitor complexes, and various protein fragments that are used as in vivo markers of activation of hemostasis. Such markers (e.g., F1 + 2 as a marker of in vivo thrombin generation and D-dimer as a marker of fibrin formation and subsequent lysis) are elevated in patients with liver diseases, and although these increases are interpreted as evidence for ongoing activation of coagulation, a likely alternative explanation is that elevated levels of these makers reflect a decreased capacity to clear these markers.

Pitfalls of routine diagnostic tests of hemostasis

The net effects of the complex hemostatic changes in patients with liver diseases are still incompletely understood. Up until the change of the century, the commonly accepted dogma was that patients with liver diseases
had a hemostasis-related bleeding tendency. This dogma had a firm clinical foundation as bleeding in patients with liver diseases is common with variceal bleeding and bleeding during major invasive procedures (notably liver transplantation), as the most important bleeding events. The observation of frequent clinical bleeding in patients with substantial alterations in routine diagnostic tests of hemostasis led to the conclusion that liver diseases are associated with a hemostasis-related bleeding tendency. Further clinical observation and more in-depth laboratory studies have led to a complete reversal of this dogma, which is outlined in the subsequent section. First, the pitfalls of commonly used diagnostic tests of hemostasis are discussed.

The platelet count, prothrombin time (PT), and activated partial thromboplastin time (APTT) are widely used screening tests of hemostasis. An isolated severely reduced platelet count is associated with a bleeding tendency. However, whether acquired thrombocytopenia always benefits from attempts to improve the platelet count is questionable. Spontaneous bleeding is uncommon when platelet counts are above 10,000/μL, and liberal prophylactic transfusion of platelet concentrates is increasingly discouraged in settings such as chemotherapy-associated thrombocytopenia or neonatal thrombocytopenia [26,27], although prophylaxis is required at platelet counts below 10,000/μL [28].

Prolongations in the PT and APTT are associated with a bleeding tendency when caused by individual coagulation factor deficiencies, such as the hemophilias. Deficiencies in coagulation factor XII, prekallikrein, and high-molecular weight kininogen, however, do result in prolongations of the APTT but are not associated with a bleeding tendency. The PT and APTT can also be prolonged by preanalytical errors or systemic diseases. In fact, prolongations in the PT or APTT frequently do not have (major) clinical consequences [29].

FIGURE 13.3 Causes of the hemostatic changes in patients with liver diseases. The multiple changes that either reduce or promote hemostasis can be attributed to four mechanisms. (1) A reduced synthetic capacity of the liver results in decreased levels of many proteins involved in hemostasis. Moreover, decreased hepatic synthesis of thrombopoietin contributes to thrombocytopenia. (2) Systemic intravascular coagulation results in consumption of platelets and hemostatic factors. (3) Systemic activation of endothelial cells results in increased release or production of hemostatic factors. (4) Increased platelet pooling in the enlarged spleen may contribute to thrombocytopenia. Source: Reprinted with permission from Lisman T, Porte RJ, Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116:878–885.
The platelet count, PT, and APTT are frequently used in the workup of patients undergoing invasive procedures. Indiscriminate hemostasis testing is likely of little use. For example, when patients have a structured medical history of bleeding taken, additional hemostasis testing is not helpful if this history was negative [30]. Also, patients in relatively good health or patients undergoing minor invasive procedures do not benefit from hemostasis testing as the risk of bleeding complications in these patients is exceedingly low. The need for selected hemostasis testing is exemplified by recent guidelines. For example, the National Institute for Health and Care Excellence, United Kingdom, recommends only to consider laboratory tests of hemostasis in selected patients undergoing moderate or severe surgery and in patients with an American Society of Anesthesiologists (ASA) Physical Status Classification System score of 3 or 4 (https://www.nice.org.uk/guidance/ng45/evidence/appendix-o-cg3-full-guideline-87258149466). The guidelines specifically state to consider preoperative hemostasis testing in patients with chronic liver disease and ASA 3 or 4, but as will be discussed further, this may not be very helpful. The Practice Advisory for Preanesthesia Evaluation by the ASA [31] states that “clinical characteristics to consider for ordering selected coagulation studies include bleeding disorders, renal dysfunction, liver dysfunction, and type and invasiveness of procedure.” Routine preoperative hemostasis testing may include platelet count, PT, APTT, and fibrinogen levels, although the National Institute for Health and Care Excellence guidelines specifically refer to PT and APTT testing only.

The platelet count, PT, and APTT are thus very poor predictors of spontaneous or procedure-related bleeding in patients with a negative bleeding history. In patients with a positive bleeding history, the abnormal platelet count, PT, and APTT are indicative of isolated, acquired, or congenital disorders. In other words, these tests are only useful predictors in patients with isolated deficiencies which only make up a fraction of the patients with abnormalities in these tests in routine clinical practice [29].

Why are these test such poor predictors of bleeding in the absence of isolated hemostatic disorders? To take the PT and APTT as examples, these are tests that have never been developed or intended to serve as tests that would predict bleeding. Instead these tests have been developed for diagnosing isolated coagulation factor deficiencies and for monitoring vitamin K antagonist therapy. Importantly, the PT and APTT are only sensitive for plasma levels of procoagulant factors, as illustrated in Fig. 13.4. The PT and APTT are thus insensitive for alterations in the natural anticoagulant pathways (TFPI, antithrombin, and the protein C system), which becomes relevant when the PT and APTT are used with the aim to establish the hemostatic status in patients with multiple (acquired) alterations in the hemostatic system. Variant viscoelastic hemostatic tests, for example, thromboelastography (TEG) and rotational thromboelastometry (ROTEM), are sensitive for variations in plasma levels of TFPI and antithrombin. These tests, however, are still insensitive for the protein C pathway as activation of protein C requires the endothelial cell receptor TM, which is not present in blood samples or reagents for routine hemostasis tests. In addition, the PT and APTT are tests that detect the generation of the fibrin clot. However, fibrin clot formation occurs very early in the hemostatic process, and therefore only reflects part of the coagulation process. In fact, a fibrin clot already forms in vitro when approximately 5% of the total thrombin generated during coagulation has been formed [32].

Although the platelet count, PT, and APTT are primarily designed to detect isolated disorders in patients with clinical bleeding, they are frequently used as predictors of bleeding in preprocedural workup, for which they are...
poorly suited. Many preprocedural hemostasis screens are thus not required, and when abnormal test results are found, they may very well not have clinical consequences. In more general terms, the usefulness of preoperative laboratory screening has already been questioned in 1985 [33]. It was reported that “Several tests ordered by protocol and performed by the laboratory at the time of admission were examined in these samples, including complete blood cell count, differential cell count, prothrombin time, partial thromboplastin time, platelet count, six-factor automated multiple analysis, and glucose level. Sixty percent of these routinely ordered tests would not have been performed if testing had only been done for recognizable indications, and only 0.22% of these revealed abnormalities that might influence perioperative management. Chart review indicated that these few abnormalities were not acted on nor did they have adverse surgical or anesthetic consequences. In the absence of specific indications, routine preoperative laboratory tests contribute little to patient care and could reasonably be eliminated.”

However, a recent paper demonstrated that little has changed since 1985. In around two million elective noncardiac procedures performed in the United States, 36% of patients had platelet count, PT, and APTT and only 16% of patients had no hemostasis tests done [34]. However, only 11% of patients had a history of potentially abnormal hemostasis. Although in the entire cohort abnormalities of the platelet count, PT, and/or APTT were associated with worse outcome, including periprocedural transfusion, the predictive value of a positive history was as good or perhaps even better than the predictive value of laboratory tests. The authors of this work concluded that in the absence of a positive history, preoperative hemostasis screening is not required and calculated that more than one billion US dollars could be saved annually in the United States alone, if hemostasis testing would be restricted to those with a positive history. A very similar case was made for patients undergoing neurosurgical procedures, and potential annual cost savings of 80 million euro in the United States were calculated [35].

The biggest concern of indiscriminate preoperative hemostasis testing perhaps is that clinicians are inclined to act on abnormal laboratory tests. For example, in those patients with prolongations in the PT, transfusion of fresh-frozen plasma (FFP) could be considered. However, there is very little evidence that prophylactic use of FFP reduces procedural bleeding risk in patients with abnormal preoperative PT values (which would often be in the absence of a history of bleeding) [36,37]. For example, a study of more than 1200 patients undergoing elective noncardiac surgery with an international normalized ratio (INR) of >1.5 were followed up [38]. Patients who received FFP in an attempt to improve hemostatic status were compared to patients not receiving FFP, and propensity-adjusted analyses were performed. Interestingly, the prolonged INR was not corrected in the majority of patients. However, those patients who received FFP did worse in terms of perioperative bleeding and complications including death. The increased incidence of postprocedural complications associated with prophylactic blood product transfusion may be related to transfusion-related complications such as infection, transfusion-associated circulatory overload, and transfusion-related acute lung injury [39]. These findings thus question the prophylactic use of FFP in patients with prolongations of routine diagnostic tests of hemostasis. A very similar argument can be made regarding prophylactic use of platelet concentrate in patients undergoing invasive procedures [40].

### Are liver patients really bleeders?

The classical dogma is that liver diseases are associated with a hemostasis-related bleeding tendency. Evidence for this dogma includes abnormalities in routine diagnostic tests of hemostasis and severe clinical bleeding. A frequent bleeding complication in patients with cirrhosis is variceal bleeding. However, variceal bleeding is caused by portal hypertension and local vascular abnormalities [41]. Three observations reinforce the notion that variceal bleeding is unrelated to hemostatic failure and should not be treated as a hemostatic complication. First, use of anticoagulant drugs does not appear to increase the risk of variceal bleeding [42]. Second, when variceal bleeding occurs, severity and outcome of the bleed do not appear to be different in patients who are or are not using anticoagulant drugs at the time of the bleed [43]. Third, recombinant factor VIIa, a potent prohemostatic drug, has little effect on severity and outcome of a variceal bleed [44]. In other words, exogenous modification of hemostasis does not affect risk for, or outcome of, a variceal bleed.

Another frequent bleeding event is bleeding during liver transplant surgery. When liver transplantation became available, bleeding during the procedure was tremendous and occasionally was a cause of perioperative death. The magnitude of the bleeding problem in the early days of liver transplantation is illustrated by the experience of
Laboratory changes in hemostasis

In general terms, in liver diseases there are concomitant changes in both prohemostatic and antihemostatic pathways. Initially, it was not recognized that these simultaneous changes may result in a status quo, as the hemostatic tests employed were only or largely sensitive for prohemostatic drivers. More advanced functional hemostasis tests have demonstrated that acquired defects in prohemostatic pathways are compensated for by defects in antihemostatic pathways or by “gain-of-function changes,” such as elevated levels of the platelet adhesive protein VWF. Laboratory evidence for the concept of rebalanced hemostasis has been provided both in patients with cirrhosis and in patients with acute liver failure (ALF) [51,52].

Platelets

Thrombocytopenia is common in patients with liver diseases. In more advanced cirrhosis, the majority of patients (50%–75%) have some degree of thrombocytopenia (a platelet count <150,000/μL), but severe thrombocytopenia (<50,000/μL) is relatively rare in 1%–11% [53]. The extent of thrombocytopenia increases with the severity of disease. Thrombocytopenia also frequently accompanies ALF, although the proportion of patients with thrombocytopenia is lower and the extent of the platelet count reduction is milder in patients with ALF compared to patients with cirrhosis, whereas the plasma levels of coagulation factors are much lower in ALF compared to cirrhosis [52].

The thrombocytopenia of cirrhosis is multifactorial and may include defective synthesis of TPO by the diseased liver [54], splenomegaly related to portal hypertension [55], consumption as a result of disseminated or...
localized activation [56–58], increased platelet destruction by autoantibodies directed to platelets [59], and direct bone marrow suppression by, for example, alcohol or the hepatitis C virus [60,61]. Although the liver is an important site of synthesis of TPO, decreased TPO synthesis does not appear to explain the thrombocytopenia of ALF. In fact, TPO levels are normal to increased in most patients with ALF and levels further increase during the course of the disease, despite decreasing platelet counts [62].

Recent data suggest that platelet activation/consumption is an important cause for the thrombocytopenia of ALF [63]. In an analysis of platelet count over time in patients within the ALF study group from the United States, the decrease in platelet count over time increased in proportion to the extent of the systemic inflammatory response syndrome which is common in these patients. In addition, the decrease in platelet count is accompanied by an increase in platelet-derived microparticles [64]. A similar mechanism has also been proposed to contribute to the thrombocytopenia of cirrhosis, but the presence of elevated levels of platelet microparticles in cirrhosis is controversial [65,66].

The thrombocytopenia of cirrhosis and ALF has been proposed to be compensated, at least in part, by highly elevated plasma levels of the platelet adhesive protein VWF [13,67]. Even though VWF appears to be functionally defective in that it has decreased capacity to bind its ligands collagen and platelet GPIbα, the quantitative increase dominates. Specifically, the increased plasma levels of VWF result in increased capacity to attract platelets to the site of vascular injury, at least as studied in vitro models, and thereby compensate for the decreased platelet count. In addition to high VWF levels, levels of the protease that regulates VWF and ADAMTS13 are decreased.

VWF is a multimeric protein, with increased capacity to interact with platelets with increasing multimeric size. VWF is synthesized as “ultra-large” multimer and immediately processed by ADAMTS13 to smaller, less reactive, multimers. This immediate processing is absolutely required since acquired or congenital deficiency of ADAMTS13 results in a severe thrombotic disease referred to as TTP. TTP is characterized by organ failure as a result of spontaneous platelet aggregation in the microcirculation driven by ultra-large VWF [5]. Confusingly, despite high VWF and low ADAMTS13 levels [68] in patients with liver diseases, the multimeric size in such patients is decreased compared to healthy individuals, which may be explained by processing of VWF by other proteases that are upregulated in liver disease (notably the leukocyte proteases cathepsin G and elastase and the fibrinolytic protein plasmin are all known to cleave VWF) [13,67,69]. The role of reduced ADAMTS13 in platelet function in patients with liver diseases is therefore incompletely understood. However, decreased levels of ADAMTS13 may promote platelet function independent of VWF multimeric size as ADAMTS13 not only processes freshly released VWF but also cleaves VWF in a growing platelet thrombus [70].

Importantly, although cirrhotic thrombocytopenia appears to be compensated for by elevated VWF levels, cirrhotic anemia may contribute to in vivo platelet dysfunction given the role of RBCs in transporting platelets towards the outer region of the blood vessel [71]. Improvement of severe anemia does not only improves tissue oxygenation but actually also has prohemostatic properties, for example, clinically evidenced in treatment of patients with renal failure with erythropoietin [72].

There is continuous debate on the functionality of platelets in patients with liver diseases. Historically, patients with cirrhosis were reported to have functional platelet defects. In the 1960s, it was already shown that platelets from patients with cirrhosis have an in vitro aggregation defect [73]. The decreased capacity to activate platelets from patients with cirrhosis in vitro has been confirmed by many laboratories [74–77]. However, more recent literature reports platelet function to be normal or even enhanced [78–80]. A major concern in published literature is the frequent use of platelet function tests that are sensitive for the platelet count of the samples, which gives unreliable results [22]. My interpretation is that platelet function is well preserved, but indirectly anemia and thrombocytopenia impair platelet function, which is in part compensated for by elevated levels of VWF.

**Coagulation and fibrinolysis**

Next to compensation of cirrhotic thrombocytopenia by elevated VWF, the low levels of procoagulants and low levels of antifibrinolytic proteins are compensated for by low levels of anticoagulants and profibrinolytics. The net result of these changes appears to be a rebalanced coagulation system and a rebalanced fibrinolytic system. Laboratory evidence for these concepts has emerged by development of functional tests of coagulation and fibrinolysis that take the interplay between all procoagulant and anticoagulant systems and fibrinolytic drives into account.

Specifically, TM-modified thrombin generation is an in vitro test that is sensitive for changes in plasma levels of all natural procoagulant and anticoagulant systems and gives a fair representation of the thrombin-generating capacity of a plasma sample. Initial studies demonstrated comparable thrombin generation using the TM-modified test [81], but subsequent studies by other groups frequently reported higher thrombin generation in
patients compared to controls [10,82–85]. Multiple research groups are also using this test in the absence of TM, which gives a flawed representation of coagulation potential in patients with complex changes in the coagulation system. Omission of protein C activation in testing thrombin-generating capacity in patients with changes in both procoagulant and anticoagulant systems underestimates actual thrombin-generating capacity. Also, ratios of the thrombin generation test in presence and absence of TM are frequently reported and interpreted as a measure of hemostatic capacity. However, this ratio only captures the extent to which TM is able to downregulate the coagulation system and is by no means a relevant indication of global coagulation potential. For these reasons, it is advised not to report these ratios, which are misleading and difficult to interpret, and perform and report only TM-modified thrombin generation testing [86].

Similarly, a plasma-based fibrinolysis test which is sensitive for all activators and inhibitors of fibrinolysis [87] has demonstrated fibrinolytic rebalance due to simultaneous changes in profibrinolytic and antifibrinolytic proteins in patients with chronic liver disease [88]. Importantly, this research test has clinical relevance as abnormal test results predict the risk for both venous and arterial thrombosis in the general population as demonstrated in multiple independent large epidemiological studies [89]. The concept of rebalanced fibrinolysis in cirrhosis is far from what is generally accepted. Multiple studies using similar methodology have argued a proportion of patients in are a hyperfibrinolytic state [90,91]. The counterargument is that typical hyperfibrinolytic bleeding, a delayed bleeding phenotype seen in patients with α2-antiplasmin deficiency, is uncommon [88].

Finally, the decreased plasma levels of fibrinogen appear (in part) compensated for by prothrombotic changes of the fibrin clot. There are multiple changes in the fibrinogen molecule that occur in patients with liver diseases including oxidation and changes in the glycosylation pattern. Interestingly, these changes appear to have opposite effects. Hypersialylation of fibrinogen in patients with cirrhosis has been demonstrated to impair fibrin polymerization, so that despite normal thrombin generation it takes longer for the fibrin clot to form in patients compared to healthy individuals [17,92]. However, once the fibrin clot has formed, it appears to be more thrombogenic in patients as it is less permeable to fluid [20]. Fibrin clot permeability is decreased in multiple thrombotic diseases, and more thrombogenic fibrin clots are thought to be directly responsible for increased thrombotic tendencies [93].

**Development of the concept of rebalanced hemostasis**

Thus the clinical observations of a remarkably mild bleeding tendency with an increased venous thrombotic risk in patients with chronic liver disease combined with laboratory evidence for intact platelet adhesive capacity, coagulation, clot formation, and resistance to lysis has led to the concept of rebalanced hemostasis (Figs. 13.5 and 13.6). In this concept, the “average” patient with liver disease maintains hemostatic balance, but with less “weight” on both ends of the hemostatic scale. Therefore, the patient with liver disease is in a constant struggle to maintain hemostatic balance, which explains the increased risk for both bleeding and thrombotic complications.

The concept of hemostatic balance has led to important changes in clinical management, which will be discussed further. Two important nuances to the concept, however, require discussion. First, the phrase “rebalanced hemostasis” might be too simplistic. Although there is clear compensation for defects in prohemostatic pathways by changes in antihemostatic pathways, the net result is not completely neutral. A “rebalanced hemostatic status with distinct hypocoagulable and hypercoagulable features” may be a more appropriate term. The hypocoagulable and hypercoagulable features are similar but not identical between different types of liver diseases, which will be discussed separately in sections ahead. Second, a variety of functional hemostatic tests have been used to assess the net results of the complex hemostatic changes in patients with liver diseases and these tests have all been very valuable in the development of the hemostatic rebalance concept. However, all these tests have limitations, and for most tests it is unclear whether they have any value in predicting the hemostatic status of an individual patient (i.e., is this patient more prone to bleeding or thrombosis?). The most important limitation is that all tests assess only a fraction of the entire hemostatic process. In vivo, hemostasis is an interplay between blood cells, blood proteins, the vessel wall, blood flow, etc. None of our diagnostic or research-based tests include all these components. We uniformly lack tests that include the vessel wall, many of our tests lack flow, we simplify tests by using plasma (which makes the tests easier to interpret, but dismisses the role of blood cells), and we need to admit that there are likely important components of the hemostatic system that we do not yet understand.

An example of our limited knowledge of hemostasis and thrombosis includes the role of neutrophil extracellular traps in hemostasis and thrombosis that has just only recently been recognized [96], and the role of ADAMTS13, which is a crucial protein, but only identified at the beginning of this century [97]. Also, clinical observations point towards a limited understanding of the hemostatic system. For example, a deficiency of factor VIII or IX results in
a predictable, lifelong bleeding tendency at defined tissues (muscles and joints, predominantly). However, a deficiency of factor V (which is downstream of factors VIII or IX) or even fibrinogen (the terminal player in the coagulation cascade) results in a much more unpredictable clinical phenotype, with some patients being asymptomatic for long periods of time without any treatment.

**Compensated cirrhosis**

In patients with well-compensated cirrhosis, hemostatic changes are relatively mild, but clear alterations in all hemostatic systems are apparent. When cirrhosis progresses, changes increase which are largely proportional to
severity of disease. There is mild thrombocytopenia, with a median platelet count of 120,000/μL in patients with Child A cirrhosis [10]. VWF levels are clearly elevated, with approximately threefold higher levels in Child A patients, but with only mild changes in ADAMTS13 at around 80% of normal [68,100]. Plasma levels of all hepatocyte-derived factors are mildly decreased to around 80% of normal in Child A cirrhosis and proportionally decrease further in more advanced disease [10,11]. The PT is very mildly prolonged in Child A cirrhosis and increases more substantially with progressing disease. However, even in patients with very mild coagulation changes, an increase in thrombin-generating capacity is already apparent, with maintenance of plasma hypercoagulability and increasing disease severity [10,82–85].

Fibrin polymerization is delayed in compensated cirrhosis but the clot ultimately formed is more permeable than clots of healthy individuals, with fibrinogen levels that are generally within the normal range [20]. There is continuing debate on the fibrinolytic status in patients with compensated cirrhosis. My laboratory consistently finds a normal plasma fibrinolytic potential in patients with compensated disease [10,88], which we feel is consistent with the lack of typical fibrinolytic bleeding in these patients. Other laboratories come to different conclusions and find hyperfibrinolysis proportional to disease severity, using similar experimental approaches [90,91].

**Decompensated cirrhosis and acute-on-chronic liver failure**

Hemostatic changes in patients with decompensated cirrhosis and acute-on-chronic liver failure (ACLF) are generally an exaggeration of the hemostatic status of patients with compensated disease. Specifically, moderate thrombocytopenia, strongly reduced plasma levels of hepatocyte-derived proteins, and strongly increased levels of endothelial-derived proteins such as VWF are common [101]. Little is known on platelet function and the extent of compensation of thrombocytopenia by elevated VWF in acutely ill cirrhotics. Thrombin generation potential is elevated despite very low levels of coagulation factors in some patients [101] and a mixed fibrinolytic capacity has been demonstrated with a hyperfibrinolytic state dominating patients with acute decompensation, but a hypofibrinolytic state dominating ACLF [102]. Interestingly, a hypofibrinolytic state, which is characteristic of patients with sepsis without underlying liver disease, predicted short-term mortality.

Although the aforementioned data suggest a predominantly hypercoagulable profile, studies using whole blood viscoelastic tests come to an opposite conclusion and find defective clot formation particularly in ACLF [103,104]. Which approach lies closest to the truth is unclear as very little data on incidence of bleeding and thrombosis in these patients are available. Although bleeding is common and related to indices of hemostatic failure including thrombocytopenia and low fibrinogen [105], many (major) bleeding episodes appear related to portal hypertension. Also, it is unclear whether thrombocytopenia and hypofibrinogenemia are drivers of bleeding risk or rather are markers of disease severity. Importantly, although there are clear advantages of point-of-care...
viscolastic tests over the aforementioned research-type tests (viscoelastic tests are whole blood tests, with clot formation as the endpoint), there are two important considerations. First, viscoelastic tests are sensitive for platelet count but not for plasma levels of VWF. Thus impaired clot formation by viscoelastic testing in a patient with cirrhosis is likely an underestimation as elevated VWF levels at least in part compensate for thrombocytopenia [13]. Second, viscoelastic tests are insensitive for the protein C system as no TM is present in blood or in the test reagent. Therefore, by definition, viscoelastic tests underestimate coagulation potential under conditions in which the functionality of the protein C system is decreased, such as in patients with liver diseases who have decreased levels of protein C [106].

Thus the conclusion from studies using viscoelastic tests that critically ill patients with cirrhosis have defective hemostatic capacity is not supported by the data. Interestingly, in patients with compensated disease, some studies have shown normal viscoelastic tracings in a large proportion of patients [107] and again, this may be an underestimation so that patients with compensated disease are in fact hypercoagulable also in a whole blood environment.

**Fatty liver disease**

Patients with nonalcoholic fatty liver disease (NAFLD) appear clinically more prothrombotic as compared to patients with liver diseases from other etiologies. For example, NAFLD is associated with an increased risk for cardiovascular disease and this increased risk appears independent from conventional cardiovascular risk factors [108]. NAFLD also increases the risk for venous thrombosis [109] and cirrhosis as a result of NAFLD/nonalcoholic steatohepatitis (NASH) is associated with an increased risk for deep vein and portal vein thrombosis (PVT) compared to cirrhosis of other etiologies [110,111]. The prothrombotic nature of NAFLD has been ascribed to hyperactive hemostasis [111,112]. However, since obesity and liver failure in absence of fatty livers are also associated with hyperactive hemostatic changes [113,114], it is unclear whether the prothrombotic nature of NAFLD can truly be ascribed to the fatty liver component of NAFLD. One study has measured plasma levels of individual hemostatic factors in a large number of patients with well-defined liver histology and concluded that “…our results show that NAFLD and NASH independently contribute to the prothrombotic state in obesity by an increase in PAI-1, whereas other prothrombotic factors are unaffected by liver status. This finding might, in part, explain the increased cardiovascular risk associated with NAFLD” [115]. Thus the fatty liver component of NAFLD is unrelated to most of the hemostatic changes observed, with the exception of PAI-1.

My laboratory has reported on functional studies in patients with various stages of fatty liver disease and concluded that “the overall hemostatic profile is comparable between patients with noncirrhotic NAFLD and controls. Additionally, prothrombotic features (hypofibrinolysis and a prothrombotic structure of fibrin clot) in patients with NAFLD are likely driven by obesity. Our study suggests a limited role for hyperactive hemostasis in the increased thrombotic risk in NAFLD.” [116]. Tripodi and cowokers came to a very different conclusion [112], but the problem with this study is that meaningful parameters of hemostatic capacity (e.g., TM-modified thrombin generation) were not reported. Rather, this study only reported difficult-to-interpret ETP ratios.

**Acute liver failure**

ALF is historically considered as a bleeding disorder. Indeed, in early clinical observations, spontaneous bleeding was frequent (in 50%–70% of the patients) and was the proximate cause of death in approximately 30% of the patients [117,118]. In current experience, however, spontaneous bleeding is uncommon (approximately 10%), usually gastrointestinal in origin, and is almost never the immediate cause of death [119]. Even bleeding during invasive procedures is less common than might be expected based on the substantially prolonged INR. For example, the risk of intracranial bleeding complications after insertion of intracranial pressure-monitoring devices is only approximately 10%, but clinically insignificant in half of these cases [119].

ALF is accompanied by hemostatic changes that are distinct from that of patients with chronic liver diseases. An INR >1.5 is part of most definitions of the ALF syndrome which means that patients with ALF per definition have decreased levels of hepatocyte-derived hemostatic factors [120]. Plasma levels of procoagulants and anticoagulants in ALF are generally lower compared to those in patients with advanced cirrhosis [121], and levels of endothelial-derived factors such as VWF are higher in ALF than in cirrhosis [67]. Conversely, the thrombocytopenia of ALF is much milder than that in cirrhosis [122].

III. Cardiovascular system in liver failure
Despite major abnormalities in levels of hemostatic factors, hemostatic balance appears maintained, as evidenced by normal thrombin generation and whole blood clot formation in viscoelastic tests [123,124]. Potential thrombotic features in ALF include a profound VWF/ADAMTS13 unbalance with relatively normal platelet counts and profound hypofibrinolysis [67,123]. In a large study, however, it was demonstrated that a prothrombotic VWF/ADAMTS13 phenotype was associated with bleeding rather than with thrombosis [125]. As systemic inflammation is associated with a VWF/ADAMTS13 unbalance, these findings suggest that bleeding in ALF relates more to systemic inflammation than a primary coagulopathy. Animal models of ALF have suggested that intrahepatic activation of coagulation drives disease progression [126,127] and that elevated VWF is responsible for delayed hepatic repair [128]. In addition, the profound hypofibrinolytic status may contribute to progression of liver failure by preventing clearance of intrahepatic clots and may, similarly to what has been described in sepsis, contribute to extrahepatic organ failure [129]. Whether targeted antithrombotic interventions may be beneficial in humans has not been established but, in particular, those interventions that will not induce a severe bleeding tendency will be of interest. Such interventions include administration of ADAMTS13 concentrates or blockers of VWF.

**Liver transplantation**

Additional hemostatic changes occur during liver transplantation due to hemodilution, consumption as a result of surgical injury, the anhepatic phase, and the reperfusion phase. During transplantation, plasma levels of hemostatic factors progressively decrease, with the exception of endothelial-derived proteins such as VWF that remain at relatively constant levels [130–132]. Despite further reductions in clotting factors and a consequent further increase in the PT, thrombin-generating capacity remains normal or even supranormal [131]. Maintenance of fibrinogen levels, however, appears important as the quality of the fibrin clot substantially decreases intraoperatively when fibrinogen levels become low [133]. A temporary hyperfibrinolytic state after reperfusion converts to “fibrinolytic shutdown” at the end of surgery [134].

The net effect of all these intraoperative changes is a hemostatic system that remains in balance, although hyperfibrinolysis can significantly contribute to bleeding [135]. The key role of fibrinolysis is evidenced by the clinical efficacy of antifibrinolytic drugs in this setting [136,137]. Postoperatively, a relative hypercoagulable state persists [138], which may be linked to the risk of deep venous thrombosis and thrombosis of the portal vein or hepatic artery [132]. This postoperative hypercoagulable state is characterized by a persisting VWF/ADAMTS13 unbalance, normal to elevated thrombin-generating capacity, and persisting hypofibrinolysis. Elevated VWF and a hypofibrinolytic state were still present in liver transplant recipients in stable condition at 1 year after transplantation and these hypercoagulable features have been attributed to persisting endothelial cell activation potentially mediated by immunosuppressive drugs [139].

**Bleeding in liver diseases**

In discussing bleeding complications in patients with liver diseases, it is of paramount importance to define the likely instigator or driver of the bleed. In typical “bleeding disorders,” such as hemophilia, hemostatic failure is the driver of both spontaneous and provoked (e.g., procedure-related) bleeding. In these cases, management of bleeding simply relies on correcting the hemostatic defect (infusion of FVIII or IX concentrate in case of hemophilia A or B, respectively) and/or providing an alternative form of hemostatic therapy (local measures, antifibrinolytic therapy, or so-called “bypassing agents” in case of inhibitor-complicated hemophilia).

However, in patients with liver diseases in which, as I have previously argued, a true “bleeding disorder” is not present, spontaneous and provoked bleeds have many potential causes. First, portal hypertension is the driver of variceal bleeds and since variceal bleeds are neither instigated nor aggravated by anticoagulant drugs [42,43], it is unlikely that hemostatic failure contributes significantly. Second, portal hypertension is also likely the driver of a proportion of bleeds during invasive procedures [49]. Third, procedural bleeds may be caused by inadvertent puncture of vessels (e.g., a bleeding at a paracentesis puncture site [140] or a “surgical bleed,” i.e., during liver transplantation). Fig. 13.7 summarizes the three causes of bleeding in patients with cirrhosis.
Portal hypertension:
Bleeding from esophageal varices

Bleeding from procedures & incisions
Mechanical Insult and Trauma

Bleeding from puncture sites (A),
Mucosal bleeding, & Bruising (B).
Clot weakness & breakdown

Dental bleeding:
Hemostatic Failure and trauma

Portal Hypertension:
Gastropathy

Bleeding in liver diseases

III. Cardiovascular system in liver failure
Incidence and pathogenesis

It has not been established how frequent hemostasis-related bleeds in patients with cirrhosis occur, which in part is a consequence of misclassifications of hemostatic bleeds in this patient population. A large proportion of bleeds that are likely related to hemostatic failure in patients with cirrhosis is cosmetic or mild and does not require hemostatic intervention. Such bleeds include bruising, gum bleeds, nose bleeds, menorrhagia, and bleeding from puncture wounds. Clinically relevant spontaneous bleeds, such as intracerebral hemorrhage, seem to occur at similar or perhaps slightly increased rates in patients with liver diseases compared to those without [141,142]. Beyond variceal bleeds, bleeding episodes in patients with cirrhosis, which are a potential clinical concern, are frequently procedure-related bleeds. Interestingly, the incidence of procedure-related bleeds is much smaller than perceived by clinicians [143], likely because of the dogma of liver disease as the prototype of acquired bleeding disorder, the memory of frequent massive transfusions during liver transplantation, and the clinical reality of frequent variceal bleeding. Bleeding risk in common procedures such as liver biopsy, paracentesis, thoracentesis, and hepatic-venous pressure gradient measurements is less than 1% (reviewed in [143]). Bleeding risk appears higher with complex dental procedures, variceal band ligation, and endoscopic polypectomy but the bleeding risk in these “high-risk” procedures is still well below 10% (reviewed in [143]).

Bleeding complications are generally not predicted by laboratory values which means that the risk of a bleed is as large as in a patient with laboratory evidence of coagulopathy than a patient without it (i.e., prolonged PT/INR and/or thrombocytopenia). Some studies have reported increased risk of procedural bleeds in those with laboratory evidence of coagulopathy [105,144], but it might be that this relation is not causal and that increased severity of illness increases bleeding risk. In addition, procedural bleeding risk appears dependent on experience and on the use of imaging to avoid vessel puncture during procedures such as biopsy and paracenteses also likely reduces bleeding risk. Taken together, clinically significant spontaneous or procedure-related bleeding in patients with cirrhosis is rare and often unrelated to hemostatic failure. This statement aligns with clinical observations in liver transplantation. This lengthy, invasive procedure can be performed without any requirement of blood products, regardless of the preprocedural PT/INR and platelet count [145]. The proportion of patients that undergoes transfusion-free liver transplant surgery varies tremendously between centers, which may be in part related to the case mix, but is likely also a consequence of differences in surgical and anesthesiological skill and technique. Transfusion-free transplantation requires active fluid restriction, meticulous surgical hemostasis, and optimal anesthesiological management. (Refer Chapter 18 for discussion of other anesthesia considerations in liver transplantation.)

Prevention

Prevention of procedural bleeds has long relied on a proactive prohemostatic approach aimed at normalization of abnormalities in the PT/INR and platelet count. However, there is very little evidence that prophylactic administration of FFP and/or platelet concentrates reduces bleeding risk but there is evidence to suggest it is harmful [36,146–149]. Given that there is abundant evidence that hemostatic balance is preserved in even the sickest patients with liver diseases, the low to very low bleeding risk of many common procedures, and the side effects of blood product transfusion, we have proposed that the majority of patients will benefit from a “wait-and-see” approach, in which prohemostatic therapy is only administered in case of active bleeding. This approach is widely adopted during liver transplant procedures and because liver transplant teams accept prolongations in PT/INR and/or platelet count, it is now possible to perform liver transplant procedures without the requirement for any blood products.

Arguments against prophylactic FFP or platelet concentrate infusion include the following:

1. Although FFP improves plasma levels of individual coagulation factors to some extent, the overall (ex vivo) hemostatic balance is not changed because of the simultaneous infusion of procoagulants and anticoagulants [150].
2. The yield of platelet concentrate is low and results in very little improvement of (ex vivo) hemostatic status [151].
3. FFP and platelet concentrate are high-volume products, which carry the risk of volume overload, particularly in patients with compromised cardiac output, and results in increased systemic and portal pressure [152]. Avoidance of exacerbation of portal hypertension is essential as portal hypertension itself is an important driver of procedural bleeding.
4. Blood products are associated with various transfusion-related side effects and some of these are particularly relevant for patients with liver diseases. For instance, in patients with liver diseases, the risk for transfusion-
associated acute lung injury is higher compared to transfused patients without any underlying liver disease [148,149]. Also, platelet transfusion has been suggested to exacerbate immune dysfunction in patients with cirrhosis [153].

5. Blood products (and the potential side effects) are associated with significant health care costs [154].

6. Blood products might “fuel the fire,” not only by exacerbation of portal hypertension but also by increasing intravascular or intrahepatic clot formation that could exacerbate hepatic or extrahepatic organ failure [114].

Patients that might be eligible for prophylactic blood product transfusion are those undergoing procedures in which a bleeding complication may cause irreparable damage (e.g., placement of an intracranial pressure monitor in a patient with ALF) or patients with a history of (hemostasis-related) spontaneous or procedure-related bleeding. Nevertheless, there is little evidence that there is a net beneficial effect in these selected patients.

Although there is no relation between PT/INR and procedural bleeding risk [155–157], there are studies suggesting that thrombocytopenia and/or hypofibrinogenemia are associated with an increased bleeding risk [105,144]. However, since many bleeding complications in these studies appear unrelated to hemostatic failure, it might very well be that the hemostatic abnormalities reflect severity of liver disease rather than being direct drivers of bleeding risk. Would this be true, correction of the hemostatic abnormalities by infusion of platelet concentrate of fibrinogen concentrate would not decrease bleeding risk (and platelet concentrate might even increase the risk because of the effects of fluid infusion on portal pressure). Indeed one study has suggested a lack of benefit of fibrinogen suppletion in critically ill patients with cirrhosis [158].

In aggregate, there is very little evidence that prophylactic infusion of FFP or platelets is beneficial in prevention of spontaneous or procedure-related bleeding in patients with liver disease. There is evidence that FFP and platelet concentrate do not improve ex vivo hemostatic status in a meaningful way, and there is evidence that these blood products may do harm. Notably, common procedures such as paracentesis, thoracentesis, and variceal ligation have a low bleeding risk and are unlikely to benefit by any prophylactic procoagulant measures, as outlined in recent guidance documents [159–163]. Importantly, the experience of the operator is a determinant of bleeding risk as, for example, documented in studies on liver biopsy [164], as is the use of image guidance, for example, during catheter placement [165]. Of note, even though procedures with a bleeding risk of >1.5% have been categorized as high risk, this means that even if prohemostatic measures would reduce bleeding risk, the number needed to treat would be substantial. Nevertheless, prophylactic FFP or platelet transfusions are common but only appear to reassure the clinician (“I have treated abnormal laboratory tests”). In addition, medicolegal considerations appear an important driver of prophylactic blood component transfusion [166].

Patients for whom the procedures are not urgent, alternative ways to improve the platelet count have been applied. A randomized trial studying the TPO-receptor agonist eltrombopag in the preprocedural setting was terminated early because of an excess of thrombotic events in the eltrombopag arm [167]. A caveat of this study, however, was the elevation of platelet counts to normal or even supranormal levels, which in combination with the high VWF and low ADAMTS13 levels may indeed be prothrombotic [168]. In subsequent studies using avatrombopag [169], lusutrombopag [170], and romiplostim [171], the increase in platelet count was much more modest. Although these studies showed that pharmacological interventions that increase the platelet count in patients with cirrhosis is safe, these studies did not demonstrate a reduction in procedural bleeding risk and therefore it is uncertain whether these drugs have a relevant impact.

It may be that more potent prohemostatic therapies are effective in a prophylactic setting, perhaps in selected patients at higher risk. Such patients include patients with a positive bleeding history or patients with additional hemostatic stressors such as infection or renal failure. More similar effective prohemostatic therapies include the low-volume coagulation factor concentrates recombinant factor VIIa (rFVIIa), fibrinogen concentrate or cryoprecipitate, and prothrombin complex concentrates (PCCs). rFVIIa has been used in the prophylactic setting in liver transplantation, but these studies showed little benefit, as did studies examining rFVIIa in acute variceal bleeding [44,172,173]. As in vitro experiments also demonstrated little effect of rFVIIa on hemostatic capacity in plasma from patients with cirrhosis [174], there is likely no role for this drug in the prophylactic setting.

In contrast, in vitro studies have demonstrated clear prohemostatic effects of PCCs and fibrinogen concentrate in plasma from patients with cirrhosis [174]. Importantly, PCCs appear more potent in plasma from patients with cirrhosis compared to plasma from healthy individuals, which may suggest PCCs need to be conservatively dosed. Although in clinical practice improvement of hypofibrinogenemia in patients with cirrhosis is deemed important, no well-designed clinical studies have addressed efficacy or safety. Nevertheless, there are some centers that have adopted a policy of PCC and fibrinogen use guided by viscoelastic testing during liver transplantation [175]. Results of this strategy suggest safety and efficacy of this approach.
Antifibrinolytic therapy is commonly used to reduce blood loss during liver transplantation. In a randomized controlled trial, patients receiving aprotinin during liver transplantation experienced up to 60% less blood loss and required up to 37% less RBC transfusions compared to patients receiving placebo [136]. Also other antifibrinolytic drugs (tranexamic acid and ε-aminocaproic acid) appear to reduce bleeding during liver transplantation [176]. A meta-analysis demonstrated that the use of aprotinin was not associated with increased thrombotic complications during or after liver transplantation and it was concluded that aprotinin was safe and effective in reducing blood loss in patients undergoing liver transplantation [137]. Aprotinin was withdrawn from the market after concerns of mortality associated with its use during cardiac surgery were raised [177]. Importantly, discontinuing the routine prophylactic use of aprotinin during liver transplantation resulted in increased blood loss in centers that did not switch to an alternative antifibrinolytic [178], but not in centers that did [179]. Overall, these results indicate that bleeding during liver transplantation is in part likely attributed to hyperfibrinolysis. As the use of antifibrinolytic therapy is safe and effective, antifibrinolytics may be used to treat or prevent hyperfibrinolysis in patients undergoing liver transplantation.

A final prohemostatic agent that is sometimes considered in patients with cirrhosis is 1-deamino-8-D-arginine vasopressin (DDAVP). DDAVP is a widely used prohemostatic agent applied in mild von Willebrand disease and mild hemophilia and in congenital platelet disorders [180]. DDAVP has been shown to correct the skin bleeding time, which is an outdated invasive test of platelet function, in patients with cirrhosis, which suggests that it may also have prohemostatic activity in this patient population [181]. Not much is known on the mechanism by which DDAVP would shorten the bleeding time in cirrhosis. The efficacy of DDAVP in patients with mild hemophilia A or type 1 von Willebrand disease has been ascribed to an elevation of circulating levels of VWF and factor FVIII [180]. However, since VWF and FVIII levels in cirrhosis are already substantially elevated [13], it is unclear whether a further elevation in levels would exert any relevant prohemostatic effect. We have demonstrated that a DDAVP infusion fails to elevate VWF plasma levels and only marginally improved ex vivo tests of primary hemostasis in patients with compensated cirrhosis, whereas robust changes were observed in patients with mild hemophilia A [182]. These findings align with a lack of clinical efficacy in patients with bleeding varices and in patients undergoing liver transplantation [183,184].

**Treatment**

As patients with cirrhosis generally have adequate hemostatic competence and as bleeding complications may be unrelated to hemostatic failure, prohemostatic therapy is not the first line of management in bleeding patients with cirrhosis, even in the presence of markedly abnormal platelet counts and/or prothrombin times [165]. When active bleeding occurs, prohemostatic treatment is only indicated when other causes for bleeding, notable pressure-related bleeds, and surgical bleeds have been ruled out.

A surgical bleed, that is, bleeding from surgically damaged veins or arteries, requires local sutures, cauterization, and/or use of topical hemostatic agents [185,186].

Treatment of portal hypertension-related bleeds should be aimed at controlling the bleed and decreasing the pressure, and specific prohemostatic therapy is not indicated [41]. Recombinant factor VIIa has been trialed in variceal bleeding but appears ineffective with a potential risk of harmful side effects [187]. Importantly, it is debatable whether a massive portal hypertensive bleed should result in initiation of a massive transfusion protocol in which balanced administration of RBCs, FFP, and platelet concentrate is administered or whether FFP and platelet concentrate should be minimally used [188]. A recent study suggests that FFP is not effective and may be harmful in treating variceal bleeding [189]. A massive transfusion protocol may also contain tranexamic acid, which has been shown to reduce death due to bleeding in trauma and postpartum hemorrhage [190,191].

Tranexamic acid (TXA) for significant gastrointestinal bleeding has recently been studied in the Halt-IT trial [192]. This large randomized placebo-controlled trial was designed to study the effects of tranexamic acid on mortality in patients with a variety of gastrointestinal bleeds. Part of the cohort had liver disease and variceal bleeding (approximately 45%). At variance with the beneficial effects of tranexamic acid observed in trials on bleeding associated with trauma and postpartum bleeding and at variance with a meta-analysis of smaller studies in gastrointestinal bleeding, Halt-IT found no mortality benefit in patients with gastrointestinal bleeding including those with variceal bleeding. Importantly, patients receiving tranexamic acid had increased incidences of seizures and venous thromboembolic events (VTE). The lack of clinical effect of tranexamic acid in variceal bleedings in patients with liver diseases may be explained by the notion that these bleedings are unlikely to be related to hyperfibrinolysis but presumably attributable to portal hypertension and/or local abnormalities in vascular...
and emergency settings<br>anatomy. In addition, it may be that patients with variceal bleeds are frequently hypofibrinolytic, as we have demonstrated in a proportion of critically ill cirrhosis patients [102]. Finally, as TXA appears only effective as a prohemostatic when given early after onset of bleeding (within 3 hours) [193], this may also explain the failure of TXA in variceal bleeding as the time from onset of bleeding to treatment in the Halt-IT trial was frequently substantially longer than 3 hours.

It has been well established that there is a benefit of restrictive RBC transfusion in variceal bleeds, which may very well be attributed to effects on portal pressure. Would RBC transfusion in this setting be accompanied by FFP and platelet transfusion, there will be undesired increases in portal pressure, limited effects on hemostatic status, and likely no effect on cessation of bleeding, which does not depend on a competent hemostatic system.

It should be noted that nonhemostatic bleeds can turn into hemostatic bleeds if the bleeding is not stopped promptly, due to massive consumption and dilution of hemostatic factors. Laboratory testing in patients with portal hypertension-related bleeds or surgical bleeds are not directly useful for clinical management. However, baseline testing may be useful in those patients in which bleeds are difficult to control to objectify that a nonhemostatic bleed is turning into a hemostatic bleed.

In patients with a hemostatic bleed or in a bleed wherein a hemostatic component is suspected, prohemostatic therapy is the primary management modality. In addition, factors such as temperature, pH, and ionized calcium concentration should be optimized as abnormalities in these factors, for example, encountered during liver transplantation, and have antihemostatic effects [47]. Notwithstanding the limitation of the platelet count and PT/INR, these tests may be useful in actively bleeding patients in deciding whether platelets and/or the coagulation system require improvement.

In many centers, correction of platelet count or a prolonged PT/INR will be by infusion of platelet concentrate or FFP. It is important to note that the yield of platelet concentrate may be low in patients with liver diseases [151]. Also, platelet function is dependent on RBCs with decreased platelet margination in anemia [2]. Thus RBC transfusion also has prohemostatic effects and hematocrit should be considered in actively bleeding patients [71]. FFP leads to improvement of the PT/INR and individual coagulation factors but the effect of ex vivo hemostatic potential is limited [150]. It should be noted that FFP is recommended in patients that are actively bleeding and have an INR >1.5, but guidelines also state that “fresh-frozen plasma has been the component of choice to manage the coagulopathy of bleeding, but there is little high quality data to inform optimal replacement of coagulation factors in major bleeding” [194]. In other words, we are unsure whether FFP infusion is the best practice in bleeding patients with a prolonged INR, and the observation that FFP does not improve ex vivo hemostatic potential also in bleeding patients may suggest that alternative prohemostatic strategies may be more effective. Such alternatives include low-volume prohemostatics such as fibrinogen concentrate, prothrombin complex concentrate, and rFVIIa. Limited clinical experience suggests fibrinogen concentrate and PCCs to be effective [175,195], which aligns with clear prohemostatic effects of these drugs in vitro [133,174]. The role of rFVIIa is unclear. Although it has been used in patients with ALF and in patients with intractable bleeding with mixed clinical success [196–198], the lack of clear clinical benefit in randomized studies in patients with liver diseases and the lack of clear effects on in vitro hemostatic potential may limit its clinical utility [44,172,173]. Antifibrinolytic agents may also be effective in patients that are actively bleeding from sources other than the gastrointestinal tract. Importantly, antifibrinolytics are not only effective in patients with overt hyperfibrinolysis but also contribute to hemostasis in patients without clear fibrinolytic disorders, for example, patients with von Willebrands disease [199]. However, as the Halt-IT trial demonstrated harm of tranexamic acid in patients with gastrointestinal bleeding, cautious use of antifibrinolytics in other settings is warranted. Having said that, the safety of antifibrinolytics in liver transplantation is reassuring [137].

Alternative monitoring strategies in patients with active bleeding are increasingly used in patients with liver diseases. Notably, viscoelastic tests may be helpful in determining whether there is a hemostatic defect and specific viscoelastic tests can determine whether the defect is primarily in platelets, coagulation, or fibrinogen [200–202]. The use of viscoelastic tests have been demonstrated to decrease blood product use in both elective and emergency settings [203–205], as viscoelastic tests are more frequently within normal ranges in liver disease patients as compared to routine diagnostic tests such as platelet count and PT/INR [107,206]. Although the general interpretation is that viscoelastic tests are much closer to the true hemostatic status of a patient compared to platelet count and PT/INR tests, there are important caveats in viscoelastic testing, as discussed in the section on “pitfalls of routine hemostasis tests.” Nevertheless, hemostatic treatment of actively bleeding patients guided by viscoelastic testing is likely the best available strategy at the moment, although it is incompletely clear whether the treatment should be primarily based on blood component transfusion or infusion of concentrates.
Thrombosis in liver diseases

Local and systemic thrombotic complications may occur in patients with liver diseases [207,208]. Historically, patients with liver diseases were considered to be “auto-anticoagulated” based on their prolonged PT and low platelet count [209], but we now know that the true hemostatic status of patients with liver diseases is a hemostatic balance with distinct hypercoagulable features that may increase the risk for thrombotic complications. This section will discuss macrovascular thrombotic complications, notably PVT, deep venous thrombosis and pulmonary embolism (PE), and myocardial infarction and stroke. The next section will deal with microvascular intrahepatic thrombotic complications and the potential consequences of these for progression of liver disease.

Incidence and pathogenesis

Portal vein thrombosis

PVT is a very rare event in the general population but a relatively common complication of cirrhosis [210]. I will limit the discussion here to cirrhotic PVT. In general, individuals become at risk for the development of venous thrombi by (1) changes in the composition of the blood, (2) changes in the vessel wall, and (3) decreases in blood flow (i.e., Virchow’s triad [211]). In patients with cirrhosis, there are clear changes in the composition of the blood [21], activation of the endothelium which presumably also affects the endothelium in the portal vein [212], and decreases in portal blood flow [213]. Nevertheless, there is continuing debate on risk factors and pathogenesis of cirrhotic PVT. Although some studies clearly indicate reductions in portal flow to be a key determinant [9,210,213,214], others have implicated hypercoagulable factors to form risk factors (e.g., carriership of prothrombotic mutations such as factor Vleiden) [215]. There is agreement that the risk of PVT development increases with increasing severity of disease and the available data suggest that patients with advanced cirrhosis likely have an annual incidence of PVT of 10%–15% [207].

PVT is an unusual thrombotic event for a number of reasons. First, there are notable distinctions between veins, for example, in the leg and the portal vein. Unlike most veins, the portal vein does not drain into the heart. Rather, it is part of a portal venous system that delivers venous blood into another capillary system, the hepatic sinusoids of the liver. Also, the portal vein lacks venous valves [216] that are clearly implicated in pathogenesis of deep vein thrombosis (DVT) [217]. Thus the environment in which the thrombus develops is different from that of thrombosis development in other venous sites. Second, PVTs are frequently asymptomatic and discovered incidentally during planned imaging studies for hepatocellular carcinoma surveillance. Thrombi may be present in the portal vein for weeks or months before they are detected, which is very different from venous thrombi at other sites that are symptomatic and are detected and treated within hours to days. Third, spontaneous resolution of PVT appears common [210,218,219]. Although symptomatic DVTs require treatment, there are indications that asymptomatic venous thrombi in the leg are relatively common, and these asymptomatic thrombi are thought to resolve spontaneously by endogenous fibrinolytic activity [220–222].

A recent study revealed the perhaps surprising finding that portal vein thrombi obtained during liver transplant surgery frequently do not contain hemostatic components such as fibrin or platelets [223]. Instead, it was shown that portal vein thrombi consisted of collagenized material that presents as intimal hyperplasia of the portal vein. In some patients, a true clot consisting of fibrin and platelets was present on top of this thickened intima (Fig. 13.8). It was also demonstrated that portal vein intimal hyperplasia was already present in a much milder form in patients with cirrhosis without PVT, but not in healthy livers or livers from patients with acute liver failure. These results thus suggest that intimal thickening (and not clot formation) leads to development of PVT and that strategies preventing progression of intimal thickening may be relevant in prevention or treatment of PVT. Interestingly, activation of coagulation has an important role in intima hyperplasia in other vascular beds. Thus, although hypercoagulability and clot formation may not be central in PVT development, there may be an important secondary role of activation of coagulation. As a PVT primarily consists of intimal thickening, the term ‘portal vein thrombosis’ may be a misnomer, and ‘portal vein stenosis’ or ‘non-malignant portal vein occlusion’ may be more appropriate. These results may also explain why anticoagulant therapy frequently fails to lead to complete recanalization, as only those portal vein thrombi with fibrin-rich sections may be susceptible to anticoagulant therapy.
Venous thrombosis

DVT and PE may occur in patients with cirrhosis. Large epidemiological studies have shown that liver diseases in fact increase the risk for DVT and PE approximately twofold [50]. Although this increased risk may relate to the relative hypercoagulable state of patients with liver diseases, it needs to be noted that chronic endothelial activation and stasis may also contribute. Stasis induced by hospitalization or immobilization for other reasons (such as a plaster cast) are well-known risk factors for venous thrombosis [224] and it should be noted that patients with cirrhosis may be more immobile as a result of their illness and are more frequently hospitalized than age-matched individuals in the general population.

Arterial thrombosis

Patients with cirrhosis are not protected from arterial events such as myocardial infarction [225] and ischemic stroke [226]. Cardiovascular disease is not uncommon in patients with advanced cirrhosis [227] and it is thought that arterial risk of patients with cirrhosis is increasing due to the increasing prevalence of cirrhosis as a consequence of fatty liver disease [228]. Fatty liver disease has a clear cardiovascular risk component with obesity, diabetes, and dyslipidemia being established risk factors for cardiovascular disease in the general population. Although specific cirrhosis-associated risk factors exist is unknown, cirrhosis-associated lipid profile changes or endothelial activation associated with cirrhosis could likely lead to progression of atherosclerotic lesions and thereby increase arterial thrombosis risk. Moreover, by a mechanism that remains unclear, the systemic inflammatory phenotype associated with NASH seems to promote increased vascular atherogenesis [229].

Prevention

Portal vein thrombosis

PVT (refer also in Chapter 4: Drugs at the crossroads of heart and liver: part 1 amiodarone) has been referred to as a “predictable milestone in cirrhosis” [230]. Theoretically, one could argue that all patients that pass a certain risk threshold would be candidates for prophylactic therapies. In a single, small, randomized trial, long-term administration of anticoagulant therapy was very effective in preventing PVT development [231]. However, this trial requires confirmation and a discussion whether the potential benefit of PVT prevention outweighs the bleeding risk associated with anticoagulant therapy. There is ongoing debate whether PVT results in disease progression [232] or whether PVT is merely an indicator of severity of disease [210]. If PVT indeed results in progression of disease, prevention of PVT would have obvious clinical benefit, whereas this benefit is less obvious if we consider PVT to be an innocent bystander. Although the aforementioned clinical trial showed that long-term anticoagulation not only prevents PVT but also delays decompensation and death, this does not necessarily imply that prevention of PVT is directly beneficial to reduce disease progression. Anticoagulation also might be able to prevent microvascular intrahepatic clot formation, which has also been implicated as a driver of disease progression (as will be discussed in the next section).
Venous thrombosis

As patients with cirrhosis are at increased risk for DVT, prophylactic administration of anticoagulants should be performed in situations when thromboprophylaxis would be indicated in the general population [233]. Such situations include major surgery, trauma, immobilization, and active cancer. It should be noted that guidelines for thromboprophylaxis are changing over time due to better insights and the availability of new-generation anticoagulant drugs.

The decision to administer chemical thromboprophylaxis is based on an estimation of thrombotic and bleeding risk. In the general population risk prediction tools such as the Padua risk score for thrombosis risk prediction and the improve bleeding risk score are used to identify patients that benefit from thromboprophylaxis during hospitalisation [234]. In patients with cirrhosis, the Padua risk score seems to identify patients at risk [235,236]. Bleeding risk scores have not yet been assessed in patients with cirrhosis and interpretation of these risks might not be entirely straightforward. Notably, liver disease defined as an INR >1.5 is part of the improved bleeding score [237] and it is questionable whether a prolonged INR in these specific patients indeed increases the risk for anticoagulation-related bleeding. Indeed, observational studies have demonstrated a low bleeding risk with standard thromboprophylactic regimens in patients with cirrhosis [42,236,238,239]. Interestingly, in studies on PVT, some studies even show a higher bleeding incidence in patients not receiving prophylaxis [240]. Importantly, bleeding episodes that occur in patients with cirrhosis are often unrelated to hemostatic failure but rather relate to portal hypertension. As anticoagulation may decrease liver disease progression and reduces portal pressure in animal models [241,242], a decreased bleeding risk of patients with cirrhosis on anticoagulants is mechanistically plausible.

Chemical thromboprophylaxis in patients with cirrhosis thus seems safe. However, multiple studies have shown that standard thromboprophylactic regimens did not decrease thrombosis risk [238,239]. Although published studies may not have been adequately designed or powered to detect a decrease in VTE risk, it may very well be that standard thromboprophylactic regimens are ineffective in patients with cirrhosis. In vitro studies have demonstrated profoundly altered anticoagulant potency of commonly used anticoagulant drugs in patients with cirrhosis [174,243,244]. This is not entirely surprising given the substantially altered composition of the plasma compartment. The combination of a hypercoagulable state and altered anticoagulant potency may indicate that drug-specific dosing regimens are required in patients with cirrhosis. Carefully designed clinical trials are required to establish optimal thromboprophylactic regimens for patients with cirrhosis and it is not unlikely that optimal strategies also take severity of disease into account.

Arterial thrombosis

With the increase in the prevalence of fatty liver disease, there will be an inevitable increase in patients with liver diseases who develop atherosclerotic cardiovascular disease, which eventually manifests as myocardial infarction and stroke. For decades, low-dose aspirin has been widely used as primary prevention. However, recent studies have questioned the net benefit of prophylactic aspirin and current guidance documents specifically state to avoid aspirin “in persons with increased risk of bleeding including a history of gastrointestinal bleeding or peptic ulcer disease, bleeding from other sites, age >70 years, thrombocytopenia, coagulopathy, chronic kidney disease, and concurrent use of nonsteroidal antiinflammatory drugs, steroids, and anticoagulants” [245]. In addition, this document states that “low-dose aspirin might be considered for primary prevention of ASCVD in select higher ASCVD adults aged 40–70 years who are not at increased bleeding risk” and “low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk.” Although these statements would indicate that patients with cirrhosis are not candidates for primary prevention, studies directly assessing bleeding risk and clinical benefit of primary aspirin prophylaxis have not been performed. It might be that the bleeding risk is lower than anticipated and that the clinical benefit is real due to a high incidence of cardiovascular events in this specific patient group. Therefore, carefully designed clinical studies on prophylactic aspirin in at-risk patients with cirrhosis (fatty liver disease and diabetes) may be indicated.

Atrial fibrillation is not uncommon in patients with cirrhosis and anticoagulant therapy to prevent stroke or embolization of clots to other vascular beds is indicated [246]. Given the difficulty of anticoagulating patients with cirrhosis, consultation between the cardiologist and hepatologist is recommended, in particular to avoid complications in decompensating patients or in patients that develop renal insufficiency. Although published clinical experience is scarce, there is a concern of drug accumulation in those patients receiving direct oral anticoagulants, since these drugs are cleared by the liver and kidneys. Nevertheless, a large retrospective study indicates relative safety of anticoagulation for atrial fibrillation in cirrhosis [247].
Treatment

Portal vein thrombosis

There is ongoing controversy on whether patients with PVT benefit from anticoagulant therapy. Arguments in favor of treating PVT are (1) a patent portal vein is beneficial when undergoing liver transplantation, (2) extension of the PVT may lead to serious complications including bowel ischemia, (3) anticoagulation may have benefits beyond PVT resolution (see next section on intrahepatic thrombosis), and (4) anticoagulation is safe [248]. Treatment of PVT with anticoagulant therapy should be initiated shortly after detection as it seems that the chance of recanalization is higher when anticoagulants are administered sooner [249]. It is generally recommended that optimal medical or endoscopic management of varices is initiated prior to starting anticoagulation with the aim to minimize bleeding complications. Treatment of asymptomatic PVT may not be beneficial in patients who are not transplant candidates, as there are no convincing data showing that treatment of PVT is associated with a survival benefit. Some argue that there is no evidence that the presence of PVT leads to an increased risk of complications and therefore argue against treating asymptomatic PVT [250].

Venous thrombosis

Symptomatic DVT or PE obviously necessitates immediate treatment. As will be discussed in the section “which drugs,” optimal treatment strategies for patients with cirrhosis have neither been established nor is it clear how long anticoagulant therapy should be continued. Before well-designed clinical studies have been performed, treatment of venous thrombotic events in patients with cirrhosis should be performed on an individualized basis by a multidisciplinary team.

Arterial thrombosis

Interventions in patients with cirrhosis developing myocardial infarction or ischemic stroke are also obviously required. In the general population, postintervention antithrombotic therapy, for example, by dual antiplatelet therapy, is associated with an important bleeding risk. This risk may be elevated in the cirrhotic patient with thrombocytopenia and the challenge is to balance bleeding risk and risk for rethrombosis [251,252]. Again, multidisciplinary individualized approached are indicated. In difficult cases, in which patients are bleeding but antithrombotic therapy seems mandatory to maintain vessel patency, accepting ongoing bleeding may be required as long as the bleeding does not become life-threatening.

Which drugs?

Historically, heparins and vitamin K antagonists were available for prevention or treatment of venous thrombotic events. Nowadays, direct oral anticoagulants (DOACs) are available which have clear advantages over traditional anticoagulants in the general population [253]. Specifically, heparins require intravenous (unfractionated heparin; UFH) or subcutaneous (low molecular weight heparin; LMWH) administration and UFH requires frequent monitoring and adjusting of drug levels. Vitamin K antagonists also require frequent monitoring to maintain the anticoagulant capacity (as assessed by INR measurements) within certain limits as under-anticoagulation increases thrombotic risk and over-anticoagulation increases bleeding risk. DOACs generally do not require laboratory monitoring, which not only decrease burden on patients but also may increase the risk for noncompliance.

The optimal drug and dosing regimen for prevention or treatment of venous thrombotic complications in patients with cirrhosis has hardly been studied. Heparins and, in particular, LMWH have been frequently used for management of PVT and DVT and appears to have a low bleeding risk in patients with cirrhosis [240,254,255]. Vitamin K antagonists have also been frequently used with a bleeding risk that may be increased. Importantly, it is unknown how vitamin K antagonists should be dosed in patients with cirrhosis that already have a prolonged INR as a result of their liver disease. In such patients the target INR is unclear. DOACs have been extensively studied in clinical trials but unfortunately, patients with liver diseases were excluded from all these trials. There is increasing experience with DOACs in patients with cirrhosis from uncontrolled studies in DVT, PVT, and atrial fibrillation that suggest DOACs to be safe in terms of bleeding risk [256–258]. It needs to be noted that in many studies, dose reductions have been applied as there was fear for bleeding or drug accumulation.

In vitro studies have demonstrated important changes in the anticoagulant capacity of heparins and DOACs in plasma from patients with liver diseases compared to plasma from healthy individuals [174,243,244]. Conceptually, this is not entirely surprising as the plasma environment in which these drugs are active is
completely different in the patient with cirrhosis. Although the total amount of thrombin generated in in vitro assays may be comparable or even enhanced in patients, the route to this normal thrombin generation is completely different due to the substantial changes in plasma levels of procoagulant and anticoagulant proteins. One can therefore imagine that the inhibitory capacity on thrombin generation by a fixed-dose drug is completely different when the concentration of the target coagulation proteins is profoundly altered.

We have demonstrated profoundly increased anticoagulant capacity of Dabigatran (a DOAC targeting thrombin) and profoundly decreased anticoagulant capacity of DOACs targeting factor Xa, with the changes in potency proportional to severity of disease. The potency changes of heparins were much more modest in this in vitro setting. A clinical study in which the Xa-targeting DOAC edoxaban was administered to healthy individuals and patients with Child A or B cirrhosis confirmed decreased anticoagulant capacity of this drug in cirrhosis as evidenced by a more modest decrease in ex vivo thrombin generation. Importantly, edoxaban reduced D-dimer levels (an in vivo marker of thrombogenicity) in healthy individuals, it did not decrease D-dimers in patients with cirrhosis, confirming a decreased anticoagulant potential of the drug [259]. Notably, we did not find evidence of accumulation of drug in these well-compensated patients, so the different anticoagulant responses in vivo were at equal drug levels. Whether DOACs do accumulate in patients who are more severely ill (i.e., with decreased hepatic and renal function) is unknown and in sicker patients monitoring of drug levels may be required (see next paragraph). These results therefore suggest that dose adjustments may be required with increased dosing requirements for Xa-targeting drugs and decreased dosing requirements for IIa-targeting drugs. Ideally, the anticoagulant capacity of DOACs should be monitored in patients with cirrhosis, for example, by thrombin generation or viscoelastic tests. However, it is unknown whether dose adjustments truly improve the risk–benefit ratio of these agents and clinical studies on optimal drug and dosing for the different indications is required.

Besides altered anticoagulant potency and potentially altered pharmacokinetics, issues with monitoring of anticoagulant drugs complicates anticoagulant treatment of patients with cirrhosis. UFH is monitored by APTT or anti-Xa assays, but both approaches are unreliable in patients with cirrhosis [260,261]. Specifically, the APTT overestimates and the anti-Xa assay underestimates UFH levels in patients with cirrhosis. Similarly, the anti-Xa assay underestimates LMWH levels in patients with cirrhosis. This is troublesome because when an anti-Xa assay suggest LMWH levels to be too low in a patient with cirrhosis, the clinical decision might be to increase the dose. However, the patient was in fact already optimally anticoagulated with the dose regimen that gave “falsely low” anti-Xa levels and dose escalations might thus increase bleeding risk. These monitoring issues are not present with DOAC use in patients with cirrhosis and anti-Xa or anti-IIa monitoring is therefore recommended in patients using DOACs for prolonged periods of time.

Intrahepatic thrombosis and disease progression

In animal models, liver injury appears uniformly accompanied by thrombus formation in the liver microcirculation. The first evidence for intrahepatic thrombus formation in experimental liver injury came from studies examining the effects of murine hepatitis virus infection in inbred strains of mice [262]. These studies demonstrated the presence of microthrombi within the hepatic microvasculature in areas of inflammation and subsequent tissue necrosis. Similarly, in mouse models of ALF [127] and fatty liver disease [263] and in models of cholestatic [264] and noncholestatic [265] fibrosis, intrahepatic thrombi have been demonstrated. Intrahepatic thrombi appear to drive progression of disease as anticoagulants or antiplatelet agents decrease thrombus formation and disease severity in these animal models [241,242,263,266–268].

Of particular interest are data in mice with established fatty liver disease in which treatment with anticoagulant drugs halts weight gain and progression of fatty liver disease [263]. Hypercoagulable states, such as carriage of factor Vleiden, result in faster progression of disease confirming that hemostatic status and progression of liver disease are directly linked at least in mice [269]. Confusingly, in some models of cholestasis-induced fibrosis, complete absence of platelets or fibrinogen paradoxically increases disease progression, suggesting that microthrombi may not always be harmful [270–274]. Fibrin and platelets have also been implicated in tissue repair mechanisms, which may partly explain the contradictory findings in some models [275,276].

It has been proposed that intrahepatic thrombi either drive disease progression by physical obstruction of the microcirculation with subsequent microischemia or that coagulation proteases such as factor Xa or thrombin are key in driving disease progression by their capacity to activate protease-activated receptors on cells [277]. These potential mechanisms are summarized in Fig. 13.9. Unanswered questions in these experimental settings
are the exact composition and location of the thrombi and the exact mechanisms linking thrombus formation or deposition of platelets and fibrin to disease progression.

The initiating triggers of intrahepatic deposition of platelets and activation of coagulation are incompletely known. Intrahepatic platelet deposition could be triggered by endothelial activation, collagen exposure, alterations in flow, and local thrombin formation, but experimental evidence in support of any of these mechanisms is thus far lacking. Intrahepatic activation of coagulation may be initiated by decryption of TF. TF, the natural activator of coagulation, is present on healthy hepatocytes in a form unable to activate coagulation (in an “encrypted” form). Liver injury has been shown to result in TF decryption with subsequent intrahepatic activation of coagulation [23,264].

In humans, a role of microvascular thrombus formation in disease progression was first proposed by Wanless and coworkers [278,279], although in these studies it was never demonstrated that platelets and/or fibrin were present in diseased human livers. These studies proposed the concept of “parenchymal extinction,” which refers to a process of local thrombus formation in small hepatic and portal veins causing local injury with consequent progression of liver injury. Indirect evidence for a role of intrahepatic thrombus formation to disease progression in humans comes from observational studies that suggest inherited hypercoagulability (e.g., carriership of FVleiden) to increase [280] and inherited hypocoagulability (hemophilia) [281] to decrease disease progression.

Four recent studies on aspirin use suggest that platelets may be related to progression of chronic liver diseases. The first report retrospectively studied 188 patients who had received a liver transplant for hepatitis C [282]. A substantial proportion of patients transplanted for hepatitis C have clinically significant disease recurrence, with cirrhosis in the graft within 5 years in 25%–35% of patients. Some of the patients in this multicenter cohort were on long-term aspirin treatment for prevention of hepatic artery thrombosis. In a multivariable analysis, aspirin use was associated with a 35% decreased risk of having stage F2 fibrosis on biopsy after a median follow-up of 2.7 years. A second study analyzed data from the National Institutes of Health—American Association of Retired

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FIGURE 13.9  Potential mechanisms involved in progression of liver disease by intrahepatic activation of hemostasis. (A) Intrahepatic activation of endothelial cells results in the formation of platelet microthrombi in the sinusoid. Such microthrombi result in disease progression via the results of microischemia of the downstream tissue. (B) Hepatocellular injury results in decryption of hepatocyte tissue factor, the generation of thrombin (IIa), and eventually fibrin deposition in the sinusoid. (C) Concomitant activation of hepatocytes and hepatic endothelium result in the formation of platelet and fibrin-containing microthrombi in the sinusoid. (D) Thrombin generated via decryption of hepatocyte tissue factor activates hepatic stellate cells to synthesize collagen.
Persons (NIH-AARP) and Health Study Cohort representing the general population in the United States [283]. Among 300,000 individuals, 428 died of chronic liver disease (excluding hepatocellular carcinoma) during follow-up. In this cohort, aspirin users had a 50% reduced risk of death due to chronic liver disease. A third study was a cross-sectional analysis of the Third National Health and Nutrition Examination Survey (NHANES III), which contains a representative sample of the general population in the United States. In 11,416 adults who underwent ultrasonography for assessment of NAFLD, 2889 individuals were identified as having NAFLD whereas the remainder served as controls. In multivariable analysis, aspirin use was shown to be associated with a decreased risk of NAFLD, primarily among men and older individuals [284].

Also in the NHANES III study, aspirin use was associated with a decreased fibrosis score as assessed with non-invasive indices in 1856 individuals with suspected chronic liver disease [285]. Importantly, ibuprofen (which lacks antiplatelet activity) was not associated with decreased fibrosis. In addition, a population-based cohort in the Netherlands measured plasma levels of VWF in 1228 individuals. VWF levels were associated with liver fibrosis as assessed by liver stiffness measurements using transient elastography after 10 years of follow-up and associations remained after adjustment for potential confounders (https://repub.eur.nl/pub/79702/160218_Plompen-Elisabeth-Petrus-Cornelia.pdf, page 107). Importantly, these results do not necessarily mean that platelets are implicated in disease progression in humans. Aspirin has many platelet-independent effects [286] that could potentially affect progression of chronic liver disease [287].

Much less data on use of anticoagulants and progression of liver disease are available. However, a small single randomized clinical study has demonstrated anticoagulant therapy with low molecular weight heparin not only to decrease PVT but also to delay decompensation and death [288]. Although the results of this study require confirmation, these findings could potentially revolutionize the management of cirrhosis, with prophylactic long-term anticoagulation as a strategy to delay disease progression in patients with compensated cirrhosis, possibly as part of a “polypill” program as proposed previously [112]. In aggregate, intrahepatic thrombosis has been clearly demonstrated in animals with various forms of liver injury and thrombus formation appears directly linked to disease progression. It is however unclear whether unbalanced hemostasis is a key component of intrahepatic thrombus formation. In humans, it is unclear whether intrahepatic thrombosis occurs and a causal link with disease progression is yet to be demonstrated.

Hemostasis and liver regeneration

Unlike other bodily organs such as the heart or kidneys, the liver has a unique regenerative capacity [289]. In most adult solid organs, injury tends to result in scarring and functional impairment rather than regeneration and repair. The liver is an exception to this rule and full restoration of functional liver mass can occur even after substantial injury. The ultimate regenerative response of the liver occurs after a partial liver resection. Up to 70% of liver tissue can be safely removed in patients that require a partial liver resection for removal of a liver tumor [290]. Following a resection, the liver eventually regenerates to its original size. In humans, substantial regeneration already takes place after 1 week whereas regeneration virtually completes after 3–6 months [291]. In rodents, liver regeneration following a partial liver resection is even faster, with complete regeneration in mice approximately after 7 days [292]. The liver not only regenerates following physical removal of liver tissue but also regenerative responses occur when liver tissue is damaged by chronic or acute liver injury or by ischemia/reperfusion injury.

Multiple laboratories have shown that platelets are vital for liver regeneration after a partial liver resection in small animal models [293–297]. Significantly, liver regeneration after partial liver resection was shown to be substantially delayed in mice that were treated with drugs that inhibit platelet function or mice that were treated with chemotherapeutic drugs or platelet-depleting antibodies, causing almost complete thrombocytopenia. Conversely, mice in which the platelet count was increased by treatment with TPO-receptor agonists, liver regeneration was accelerated. In mice, platelet accumulate in the liver very rapidly and only appear to contribute to regenerative signals in the very early phase of regeneration. When platelet are removed prior to resection in mice, regeneration is markedly impaired, whereas regeneration is unaltered when platelet are removed 2 hours after resection, suggesting that the platelet-mediated regenerative signals all occur within the first 1 or 2 hours after resection [295]. Notably, early platelet deposition in the remnant liver has also been demonstrated in humans undergoing partial hepatectomy [298]. Platelet accumulation in the murine liver remnant is dependent on VWF [295], which may mean that platelet accumulation is governed by activation of endothelial cells and exposure of endothelial-derived VWF within the liver. Alternatively, it may be that release of VWF by platelets...
contributes to platelet accumulation. A critical role of VWF in orchestrating posthepatectomy liver regeneration has also been suggested from human studies [299].

Platelets appear also relevant for liver regeneration in humans as a low platelet count following a liver resection or liver transplantation is associated with postoperative liver dysfunction and mortality [300] and with increases in liver volume over time [301].

The mechanisms underlying platelet-mediated liver regeneration are poorly understood and some of the theories discussed in literature are based on circumstantial evidence [302]. Plausible theories and the experimental deficits will be discussed below and are depicted in Fig. 13.10.

**Delivery of growth factors**

It has long been assumed that the role of platelets in stimulating liver regeneration hinges strongly on growth factors stored within platelet granules. Following a partial liver resection in small animal models, a rapid influx of platelets in the liver sinusoids has been observed [294,295]. Platelets also cross the endothelial lining within the liver and end up in the Space of Disse or even within hepatocytes [303]. This rapid platelet accumulation in the liver has been postulated to result in excretion of growth factors which enhance the regenerative response. Such growth factors include hepatocyte growth factor, vascular endothelial growth factor, insulin-like growth factor, and serotonin. Indeed, these mitogens have been shown to enhance proliferation of cultured hepatocytes in vitro [304,305].

Compelling evidence for a role of serotonin in mediating platelet-mediated liver regeneration was provided by experiments using mice deficient in circulating serotonin [293]. However, the defective regeneration in these mice may also be explained by a defect in secondary platelet activation, as serotonin is not only a liver-directed...
mitogen but also a relevant platelet activator [306]. Indeed, inhibition of the P2Y12 receptor, which also results in defective secondary platelet activation had similar effects as circulating serotonin deficiency. A human study provided evidence for serotonin consumption following a partial liver resection and showed that a low preoperative platelet serotonin content was associated with poor outcome [307]. In this study, however, it was not examined whether the serotonin consumption following resection was related to this specific procedure or a consequence of a major abdominal surgical procedure in general. Indeed, a subsequent study in which serotonin content was compared between patients undergoing partial liver and pancreas resection provided no evidence for liver resection-specific consumption of serotonin [308].

Studies from the same group demonstrated associations between VWF and specific platelet proteins implicated in regeneration and outcome after liver resection, providing further support that VWF-mediated platelet accumulation and subsequent release of platelet molecules drive liver regeneration in humans [298,299,309].

**Delivery of platelet-derived RNA**

Since platelets are taken up by hepatocytes following a partial liver resection, it may be that platelets do not only deliver growth factors to the hepatocyte plasma membrane but also release factors involved in proliferation within the hepatocyte. An in vitro study demonstrated transfer of platelet-derived RNA to hepatocytes after platelet internalization by the hepatocyte with subsequent translation of platelet RNA to protein by the hepatocyte [303]. This “functional” transfer of RNA contributed substantially to platelet-mediated hepatocyte proliferation. However, whether platelet RNA transfer contributes to liver regeneration in vivo needs to be established. Both platelet mRNA and regulatory RNAs may play a role in platelet-mediated liver regeneration and the exact RNA species involved remain to be studied.

**Platelets as initiators of the inflammatory response**

Although it is widely assumed that platelets stimulate liver regeneration by delivery of mitogenic cargo to the liver, there is another potential explanation for the role of platelets in liver regeneration. It has been well established that liver regeneration is associated with a localized or generalized inflammatory response. Liver regeneration is impaired in mice lacking inflammatory cells or production of proinflammatory cytokines such as TNF-α [310,311]. Since platelets are well known to attract inflammatory cells [312], it is not unlikely that the role of platelet in liver regeneration is not mediated by platelets directly but indirectly by facilitation the inflammatory response. Indeed, recent work has demonstrated that platelets are key in facilitating influx of neutrophils and repair following a sterile inflammation induced by thermal injury in a mouse model [313].

**Fibrin and liver regeneration**

We have recently demonstrated that not only removal of platelets, but also removal of fibrinogen delays liver regeneration [314]. Remarkably, both fibrin and platelet accumulate in the liver remnant shortly after resection. Accumulation of fibrin is absent in thrombocytopenic mice and accumulation of platelets is absent in mice lacking fibrinogen, indicating an intricate interplay between platelets and fibrinogen in orchestrating regeneration. We identified hepatocyte TF as initiator of intrahepatic fibrin deposition after resection and demonstrated that intrahepatic fibrin deposition was also present in the early phase after liver resection in humans. Importantly, intrahepatic fibrin deposition was absent in those patients that developed postoperative liver dysfunction, suggesting that intrahepatic fibrin deposition is crucial for successful liver regeneration in humans.

These results question the vital role of platelets in liver regeneration as both the scenario that fibrin is required to attract platelets to the liver and the scenario that platelet deposition is required for intrahepatic fibrin formation are equally plausible. Both platelets and fibrin have regenerative properties and future studies should resolve this chicken and egg conundrum.

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**Conclusion**

Liver diseases are associated with complex changes in the hemostatic system that result in a rebalance in the hemostatic system. Although patients with liver diseases are at increased risk for venous thrombotic events and
may experience hemostasis-related bleeding complications, these patients are not overt bleeders or clotters. It is not yet possible to predict which patients are at risk for bleeding or thrombotic complications and it is of utmost importance to be aware of the limitations of traditional and new-generation hemostatic tests in assessing bleeding or thrombotic risk. In general terms, few patients are likely to benefit from prophylactic prohemostatic therapy and a wait-and-see approach, for example, in the context of procedures and procedural bleeding seems best practice.

Prophylactic anticoagulant therapy should not be withheld from patients at risk, although studies on risk prediction and on optimal drug and dosing regimens are required. Future studies on prophylactic anticoagulation with the aim to decrease disease progression are eagerly awaited—results from the published study on prophylactic LMWH are encouraging as this study showed marked effects on clinically relevant outcome parameters [231], but this study requires confirmation. Whether treatment of asymptomatic PVT is beneficial remains a topic of controversy, but potential additional effects of anticoagulation in delaying disease progression may be relevant in this context. Prohemostatic strategies may promote regeneration, perhaps not only after liver resection but also in patients with chronic or acute liver injury, and such strategies also deserve careful (pre)clinical studies.

Recent guidance documents outline best practices in preventing or treating bleeding or thrombosis, but it should be noted that many recommendations made in these documents rely on scarce and low-quality evidence [159–161,163].

References


III. Cardiovascular system in liver failure


III. Cardiovascular system in liver failure


III. Cardiovascular system in liver failure