Coagulation pattern in critical liver dysfunction

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Purpose of review
This article reviews the current literature dealing with pathophysiology, diagnostics, bleeding management, and thromboprophylaxis in patients with acute and chronic liver dysfunction.

Recent findings
Routine coagulation tests such as prothrombin time and International Normalized Ratio (INR) are not able to define whether a patient with critical liver dysfunction is hypocoagulable or hypercoagulable and are not able to predict the risk of bleeding in patients with liver dysfunction. Therefore, prophylactic transfusion of fresh frozen plasma and platelets in order to correct laboratory values is not appropriate. Notably, patients with liver dysfunction and increased INR are not ‘autoanticoagulated’. In contrast, thrombin generation assays in the presence and absence of thrombomodulin or Protac, a snake venom that activates protein C in a manner similar to thrombomodulin, as well as viscoelastic tests (thrombelastography/thromboelastometry) indicate that patients with liver dysfunction are rather hypercoagulable with the inherent risk of thrombosis.

Summary
Coagulopathy in patients with critical liver dysfunction is complex and can quickly decompensate to bleeding as well as to thrombosis. Both are associated with worse outcome. Hemostatic interventions should only be performed in case of clinically relevant bleeding and thromboprophylaxis should strongly be considered.

Keywords
liver cirrhosis, liver dysfunction, thrombin generation, thromboelastometry, thromboprophylaxis

INTRODUCTION
Irrespective of the underlying condition and the direct cause liver dysfunction/failure in critical care patients is characterized by hyperbilirubinemia (often), hepatic encephalopathy (in severe cases), and coagulopathy (always). The latter is defined by an International Normalized Ratio (INR) >1.5. This definition reflects the central role of the liver in hemostasis. However, recent literature has put the impact of a pathological test result on clinical features into question.

COAGULOPATHY IN LIVER DYSFUNCTION
Blood coagulation is based on complex interactions between cells and plasmatic coagulation factors with elaborated feedback mechanisms including amplifying and inhibiting loops. It is best described by the term ‘hemostasis’, highlighting the sensible equilibrium between procoagulant and anticoagulant factors as well as fibrinolytic and antifibrinolytic mechanisms.

Most of the coagulation factors are synthesized in the liver; hence, in chronic liver disease their levels are decreased. This is particularly true for the vitamin K-dependent procoagulant factors II, VII, IX, and X, as well as for factor V, but also for the vitamin K-dependent anticoagulant factors protein C and protein S, as well as for antithrombin [1\textsuperscript{st}]. Notable exceptions are the von Willebrand factor (vWF) and coagulation factor VIII, which are synthesized in the vascular endothelium and compensatorily elevated in patients with liver cirrhosis. On the other hand, the activity of the vWF cleaving enzyme ADAMTS13, a metalloprotease exclusively produced in hepatic stellate cells, is reduced in liver cirrhotic patients. Deficiency of ADAMTS13, particularly in the presence of elevated levels of large vWF multimers, increases platelet microthrombi formation and might result in sinusoidal microcirculatory disturbances and subsequent
KEY POINTS

- In patients with liver dysfunction an increased PT/INR is not necessarily associated with an increased risk of bleeding.
- Prophylactic transfusion of fresh frozen plasma and platelets should be avoided, and hemostatic interventions should only be performed in case of clinically relevant bleeding.
- Thrombin generation assays in the presence and absence of thrombomodulin or Protac as well as viscoelastic tests (thrombelastography/thromboelastometry) indicate that patients with liver dysfunction are rather hypercoagulable with the inherent risk of thrombosis.
- Patients with liver dysfunction and increased INR are not ‘anticoagulated’. Therefore, thromboprophylaxis should strongly be considered in patients with liver dysfunction.

progression of liver injury, eventually leading to multiorgan failure [2,3]. A marked imbalance between decreased ADAMTS13 activity and increased production of large vWF multimers has been shown to be closely related to functional liver capacity, hepatic encephalopathy, hepatorenal syndrome, and intractable ascites in advanced liver cirrhosis and may be useful to predict long-term survival of cirrhotic patients [3,4]. Therefore, some end-stage liver cirrhotic patients reflect conditions similar to thrombotic thrombocytopenic purpura (TTP) [3]. In transplant patients it has been shown that TTP is sometimes linked to cyclosporine A treatment. Here, cyclosporine A reduces the secretion of ADAMTS13 and leads to conformational changes in the protein structure resulting in diminished ADAMTS13 proteolytic activity [5]. Apart from sequestration of platelets in the spleen due to portal hypertension and subsequent hypersplenism [6–8] this mechanism may substantially contribute to thrombocytopenia in liver cirrhotic patients. Increased platelet adhesion and aggregation due to increased plasma levels of large vWF multimers and decreased ADAMTS13 activity seem to be rebalanced by thrombocytopenia in liver cirrhotic patients. Therefore, platelet transfusion should be restricted to bleeding complications, as it may result in further liver damage and exacerbated portal and portopulmonary hypertension [9]. Furthermore, changes in profibrinolytic and antifibrinolytic drivers have been reported. Here, plasminogen and α2-antiplasmin levels are decreased and tissue-plasminogen activator and plasminogen activator inhibitor-1 levels are increased simultaneously [1**]. Similar, but more pronounced changes of procoagulant and anticoagulant factors are observed in acute liver injury (ALI)/acute liver failure (ALF) [10**]. Recently published data report on reduced fibrinolytic activity in ALF as it has also been shown for the early phase of sepsis [11,12,13**].

Taken together, blood coagulation in liver dysfunction is rebalanced, even though on a lower level prone to tipping to thrombosis or hemorrhage depending on concomitant risk factors (Fig. 1).

COAGULATION TESTS IN LIVER DYSFUNCTION

For comprehension of the concept of balanced blood coagulation in liver dysfunction, knowledge about the scopes and limits of (the more or less routine) coagulation tests performed in the laboratory or at the point-of-care (POC) is essential.

Routine coagulation tests

The basic idea of the prothrombin time (PT), first described in 1935, was monitoring of vitamin K-antagonists (VKA) [14]. In short, the test proceeds as follows: thromboplastins of different origin are added to recalcified citrated plasma and the time until coagulation starts is measured. This procedure only mirrors the amount of procoagulant factors in plasma, but is not capable of measuring vitamin K-dependent anticoagulants (protein C and S) and the complex interaction of cells and coagulation factors in whole blood [1**]. Due to different thromboplastins results from different laboratories are not comparable. Therefore, the INR was established and is indeed useful for patients on VKA. Interestingly, the INR was adopted for many other indications, for example, estimation of bleeding risk before surgery, guidance of coagulation therapy in massive
bleeding after trauma or surgery, and also for definition of coagulopathy in liver disease. Meanwhile, it has been shown that the correlation between INR and bleeding tendency in patients scheduled for surgery is poor [15], which applies to patients with liver dysfunction as well [1*,16*]. In particular, no correlation could be observed between PT and the bleeding time observed directly on the liver during laparoscopic liver biopsy [17]. However, the validity of INR as a prognostic parameter in liver dysfunction is not affected by this finding [16*].

**Thrombin generation assays**

Thrombin generation assays are special laboratory coagulation tests, measuring the endogenous thrombin potential by at least adding phospholipids and thromboplastin to platelet poor plasma. The main parameters are lag time, velocity, and area under the reaction curve. ‘Basic’ thrombin generation is decreased in patients with liver disease. However, as the imbalance between procoagulant and anticoagulant activity in patients with cirrhosis is based on increased factor VIII and decreased protein C it can be detected by thrombin generation assays performed in the presence and absence of soluble thrombomodulin [1*,17,18]. The thrombin-thrombomodulin complex is essential to activate the vitamin K-dependent anticoagulative protein C system [1*]. In the presence of soluble thrombomodulin thrombin generation test results in patients with acute and chronic liver disease were indistinguishable from those in healthy volunteers or may even be higher [1*,13*,19]. Similar results can be achieved by the addition of Protag (PentaPharm, Basel, Switzerland), a snake venom that activates protein C in a manner similar to thrombomodulin [10*,18,20–22]. Furthermore, the results of thrombin generation assays are modified by the presence and absence of platelets [23]. Notably, platelet factor 4 modulates the substrate specificity of the thrombin-thrombomodulin complex by selectively enhancing protein C activation, while inhibiting thrombin-activatable fibrinolysis inhibitor (TAFI) activation [24]. Altogether, modified thrombin generation assays can be useful for determination of coagulation function in patients with liver dysfunction, but have the major drawback of not being available as routine laboratory tests.

**Thrombelastography/rotational thromboelastometry**

Viscoelastic tests like thrombelastography and rotational thromboelastometry (ROTEM) are performed in whole blood, mirroring the interaction between platelets and coagulation factors and, above all, the strength and stability of the clot. Here, early values of clot firmness [e.g. amplitude after 5–10 min (A5, A10)] allow for fast and reliable prediction of thromboelastometric maximum clot firmness in patients with hypocoagulability, normocoagulability, and hypercoagulability, and therefore can be used to guide hemostatic therapy in severe bleeding including patients undergoing liver transplantation [25]. Particularly intraoperatively and in critical care the short turn-around times of thromboelastometric tests (15–25 min) are an important advantage [26*]. Furthermore, the diagnostic performance of a panel of specific reagents used in thromboelastometry has been shown to be superior to monoaanalysis with kaolin-based tests [27*]. Algorithms based on the use of kaolin may lead to unnecessary transfusion of platelets [27*,28]. In contrast, algorithms based on a panel of ROTEM reagents may avoid platelet transfusion when goal-directed fibrinogen substitution would be more appropriate [27*,29,30,31*].

In patients with ALF viscoelastic tests showed normocoagulability [16*] or even hypercoagulability [10*], further challenging the concept of bleeding tendency in liver dysfunction. Notably, hypercoagulability seems to be better detected by whole blood thromboelastometry compared with thrombin generation tests using platelet poor plasma [32].

**BLEEDING MANAGEMENT IN LIVER DYSFUNCTION AND LIVER TRANSPLANTATION**

Following the concept of balanced hemostasis in liver dysfunction application of blood products and coagulation factors in order to correct laboratory values (e.g., prior to interventions) is not appropriate [1*,10*,33]. Nevertheless, fresh frozen plasma (FFP) and platelet transfusion are still used for preprocedural prophylaxis in cirrhosis patients [34,35] and liver dysfunction is one of the factors associated with greater use of prophylactic plasma transfusion in the United Kingdom [36]. However, a high proportion of current FFP transfusion are of unproven clinical benefit and have to be considered as inappropriate [37*,38*]. In severe bleeding FFP transfusion is often recommended but has to be assessed critically regarding its risks and benefits [39,40]. For correction of coagulopathy high amounts of FFP have to be applied, which often results in increased portal pressure and subsequently leads to increased bleeding and acute lung injury due to transfusion-associated circulatory overload. Therefore, intravenous fluid restriction rather than prophylactic administration of large volumes of FFP is recommended in patients with gastrointestinal bleeding.
or undergoing major liver surgery [41]. Moreover, transfusion-related acute lung injury, immunomodulation, increased nosocomial infection rates, and last but not least delay of therapy due to the thawing process have to be considered for the use of FFP [42]. Data of patients with liver dysfunction are not available yet [43,44*], but results obtained in cardiac surgery and liver transplantation prove that application of specific coagulation factor concentrates like fibrinogen and four-factor prothrombin complex concentrates (PCCs) guided by POC coagulation monitoring with thromboelastometry corrects coagulopathy goal directed without increasing the thrombotic risk [31*,45*,46*,47**]. Also transfusion of platelets could be guided by POC monitoring [27*,29,30*,31*]. If routine laboratory testing is used platelet count should be kept at about 50/µl taking into account the enhanced function described [1**,42,48]. However, platelet transfusion has been shown to be associated with a significant reduction in 1-year survival (74 vs. 92%; P < 0.001) in liver transplantation, independent of whether the platelet count was below or above 50/µl before platelet transfusion [49]. Cryoprecipitate, containing fibrinogen and factor XIII but also vWF and factor VIII, would further increase the already high levels of vWF and factor VIII possibly contributing to a procoagulant switch with subsequent thrombosis [50]. Pharmacologic agents such as antifibrinolytic drugs (e.g. tranexamic acid) or activated recombinant factor VII (rFVIIa) may be indicated in selected individuals, but these agents do not have a routine role in the management of patients with liver cirrhosis or undergoing liver surgery [41,48,51,52]. Notably, rFVIIa is not labeled for use in liver dysfunction and liver transplantation and studies have failed to demonstrate a significant benefit in bleeding of the upper gastrointestinal tract or liver transplantation [42,50,53,54*]. Keeping the potentially increased risk of thrombosis in mind, the off-label use of rFVIIa in patients with severe bleeding unresponsive to other hemostatic interventions can be considered [55**].

VENOUS THROMBOEMBOLISM IN LIVER DYSFUNCTION

In line with the above described observations patients with liver dysfunction are not ‘autoanticoagulated’ [1**,56], but, according to the findings of more global coagulation tests (thromboelastometry and thrombin generation assays), are rather hypercoagulable with the inherent risk of thrombosis [10*]. Apart from deep vein thrombosis, portal vein thrombosis, and pulmonary embolism, thrombosis can also affect the arterial system (hepatic artery thrombosis, myocardial infarction, stroke). Even the progression of liver fibrosis in chronic liver disease might be a consequence of procoagulant imbalance [1**]. Hence, venous thromboembolism (VTE) prophylaxis is required during hospitalization of patients with liver dysfunction [57*]. Nevertheless, VTE prophylaxis is still not used in about 75% of these patients [58,59].

VENOUS THROMBOPROPHYLAXIS IN PATIENTS WITH LIVER DYSFUNCTION

Basically, VTE prophylaxis can be performed by pharmacological and/or mechanical means (compression stockings, intermittent pneumatic compression) [60]. The so-called American College of Chest Physicians guidelines are updated every 4 years and present and grade the available evidence regarding thrombosis and thromboprophylaxis. Interestingly, these comprehensive guidelines do not offer any recommendation for VTE prophylaxis in patients with liver disease. This might be due to the lacking evidence, as in most studies dealing with thromboprophylaxis, patients with liver dysfunction are excluded. One recent study investigating the prevention of portal vein thrombosis in patients with chronic liver disease proved efficacy and safety of enoxaparin application (4000 U subcutaneously once daily) in cirrhotic patients [61*]. Early anticoagulation treatment in cirrhotic and noncirrhotic patients with portal vein thrombosis and acute variceal bleeding resulted in a satisfactory rate of recanalization with minimal procedure-associated morbidity [62,63]. Prophylactic use of low molecular weight heparin (LMWH) in patients with cirrhosis appears to be well tolerated [64*]. A decreased anti-Xa value in cirrhotic patients and a negative correlation with liver function challenge the unconditional use of anti-Xa assays in LMWH monitoring in cirrhotic patients and reveal a potential limitation of anti-Xa analysis in these patients. Low levels of antithrombin, because of reduced hepatic synthesis, are the most likely cause of this phenomenon [64*]. As argatroban is mainly metabolized in the liver it should be used with caution in patients with liver dysfunction [65] and/or hyperbilirubinemia [66]. Despite some absolute contraindications (e.g., peripheral vascular disease) mechanical DVT prophylaxis can be used in most patients, and is of particular benefit in patients with suspected bleeding risk. Nevertheless, mechanical DVT prophylaxis is used only in the minority of patients in the ICU [67].

CONCLUSION

Coagulopathy in patients with critical liver dysfunction is complex and can quickly decompensate to
bleeding as well as to thrombosis. Both are associated with worse outcome. However, routine plas- 
matoc coagulation tests such as PT and INR are not 
able to discriminate between hypo- and hypercoa-
gulability and are not able to predict the risk of 
bleeding in patients with liver dysfunction. There- 
fore, prophylactic transfusion of FFP and platelets 
due to an increased INR should be avoided in this 
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should strongly be considered in patients with liver 
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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have 
been highlighted as: ■ of special interest ■■ of outstanding interest
Additional references related to this topic can also be found in the Current 
World Literature section in this issue (pp. 000–000).

This review article offers a comprehensive overview about hemostatic changes in 
liver disease and their possible clinical implications.

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decreased fibrinolytic capacity in patients with acute liver injury or acute liver 

The authors demonstrate that patients with ALF/ALF have a normal thrombin 
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The authors show that despite elevated INR, most patients with ALF/ALF maintain 
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31. Görlinger K, Fries D, Dirkmann D, et al. Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. Transfus Med Hemother 2012; 39:104–113. The authors show that the implementation of perioperative POC coagulation management algorithms based on early goal-directed therapy with fibrinogen concentrate and PCC is associated with reduced transfusion requirements in different clinical settings (femoral and transplant surgery, cardiac surgery, severe trauma, and intensive care).


40. The ESA guidelines on the management of severe perioperative bleeding summarize the current knowledge in this field based on 20,664 publications from 2000 until 2012.


47. The data of this study suggest that the use of PCC and fibrinogen concentrate is effective in improving perioperative haemostasis without significantly increased thrombotic events.


49. This study showed for the first time that hemostatic therapy based on POC testing (thromboelastometry and whole blood impedance aggregometry) reduced patients’ exposure to allogeneic blood products and provided significant benefits with respect to clinical outcomes including 6-month mortality in patients undergoing complex cardiac surgery.


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55. The authors conclude that care should be taken to avoid excessive substitution with FFP, however, an accurate monitoring of patients’ coagulation status may allow thrombotic risks to be reduced.


The authors report that the prophylactic use of LMWH in patients with cirrhosis appears to be safe. A decreased anti-Xa value in cirrhotic patients and a negative correlation with liver function challenge the unconditional use of anti-Xa assays in LMWH monitoring in cirrhotic patients and reveal a potential limitation of anti-Xa analysis in these patients.

