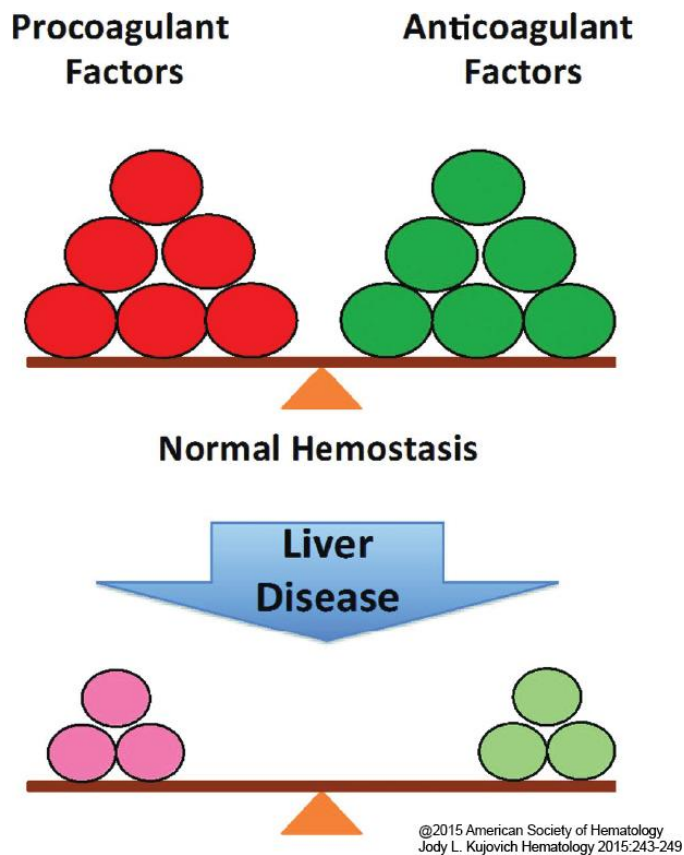


# The Coagulopathy of Liver Disease: Fair and Rebalanced?

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*This is to acknowledge that Sandra Hofmann, M.D., Ph.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Hofmann will be discussing off-label uses in her presentation.*

Biography: Sandra L. Hofmann, M.D., Ph.D. is Professor of Internal Medicine and Molecular Genetics in the Division of Hematology-Oncology. Her research interest is the post-translational modification of proteins by fatty acids and a lysosomal storage disorder caused by deficiency of palmitoyl-protein thioesterase, an enzyme discovered in her laboratory. Honors include the Jacob K. Javits Neuroscience Investigator (MERIT) Award, induction into the American Society for Clinical Investigation and Association of American Physicians and as a Fellow of the American Association for the Advancement of Science. In 2014 she received the Avanti Award in Lipids of the American Society for Biochemistry and Molecular Biology in recognition of her work on infantile Batten disease. She currently serves as attending physician on the hematology consult service at Parkland. Her clinical interests concern all aspects of benign hematology.

Purpose and Overview: To introduce the concept of rebalanced hemostasis in chronic liver disease with implications for management of clinical bleeding and thrombosis.

Learning Objectives:

- To understand that hemostasis in liver disease is rebalanced due to changes in procoagulant, anticoagulant and fibrinolytic systems.
- To appreciate that current laboratory tests have limitations for evaluating the coagulopathy of liver disease. Specifically, the PT/INR measures only procoagulant factors and is a poor predictor of bleeding risk.
- To understand why fresh frozen plasma is usually ineffective and why its use should be minimized.
- To identify modifiable triggers of active bleeding in liver disease: portal hypertension, local vascular factors, renal failure, bacterial infection, and occasionally, vitamin K deficiency and low fibrinogen.
- To recognize the increased risk of thrombosis in chronic liver disease and select candidates for anticoagulation for secondary prevention of thrombosis.

## Introduction

The purpose of this Internal Medicine Grand Rounds is to introduce the concept of rebalanced hemostasis in chronic liver disease and to provide a framework for improved recognition and management. The concept that patients with chronic liver disease have an acquired bleeding disorder is giving way to the realization that the majority are at increased risk of thrombosis, and that conventional testing has severe limitations for assessing bleeding risk and monitoring anticoagulant therapy. Clinical observations and laboratory investigations have led to the new appreciation that hemostasis is rebalanced in chronic liver disease to achieve a balanced, yet more fragile state (Kujovich, 2015; Tripodi and Mannucci, 2011; Tripodi et al., 2017).

## Historical Perspectives

*Procedural bleeding risk does not correlate with PT/INR in chronic liver disease.* The first indication that the old paradigm was incorrect came in 1981, with a report concerning bleeding time measured from the surface of the liver during 200 consecutive laparoscopic liver biopsies (Ewe, 1981). In this remarkable paper, it was shown that after needle withdrawal, the liver surface bled for an average of 4.5 minutes, with 10 patients (5%) bleeding for over 12 minutes, at which time pressure was applied and bleeding ceased. Pre-procedure platelet counts and PT/INRs were recorded, yet no correlation between the liver bleeding time and platelet count or PT/INR was observed. A later study from the Mayo clinic (McGill et al., 1990) that reported on 9,212 percutaneous liver biopsies confirmed these findings and revealed that the only risk factor for fatal bleeding was the presence of cancer (0.4% vs 0.04% mortality). No relationship to the PT/INR and only a weak correlation with platelet counts was shown.

*The risk of thrombosis is increased in liver disease.* A number of observational studies have demonstrated an increased risk of venous thromboembolism in chronic liver disease, the largest of which was a nationwide case-control study performed between 1980 and 2005 in Denmark. Nearly 100,000 patients with venous thromboembolism and 500,000 controls were compared. The relative risk for unprovoked venous thromboembolism was between 1.8 and 2.4, and was the same for cirrhotic and non-cirrhotic liver disease (Sogaard et al., 2009).

*The balance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis.* The lack of correlation between bleeding risk and conventional laboratory parameters, and the observed increased risk of thrombosis in patients with cirrhosis led Italian investigators, under the direction of Dr. Pier Mannucci at the University of Milan, to perform more detailed investigations of known clotting factors in plasma from 134 cirrhotic patients and a similar number of controls (Tripodi et al., 2009). While confirming that the plasma coagulation factors were decreased (Fig. 1), they observed that a new measure, the “endogenous thrombin potential” (which measures the amount of thrombin released when phospholipid-reconstituted recombinant tissue factor is added to platelet-poor plasma) was actually slightly increased in cirrhotic as compared to normal patients (Fig. 2). Furthermore, the addition of thrombomodulin (a factor that is not normally contained in plasma, and activates protein C) had less effect on cirrhotic plasma, similar to plasma from patients with protein C deficiency. They further showed that activated protein C activity was reduced in the cirrhotic patients and later that addition of protein C corrected the exaggerated thrombin generation

in plasma (Tripodi et al., 2013) (Fig. 3). These findings led directly to the concept of “rebalanced” hemostasis in chronic liver disease.

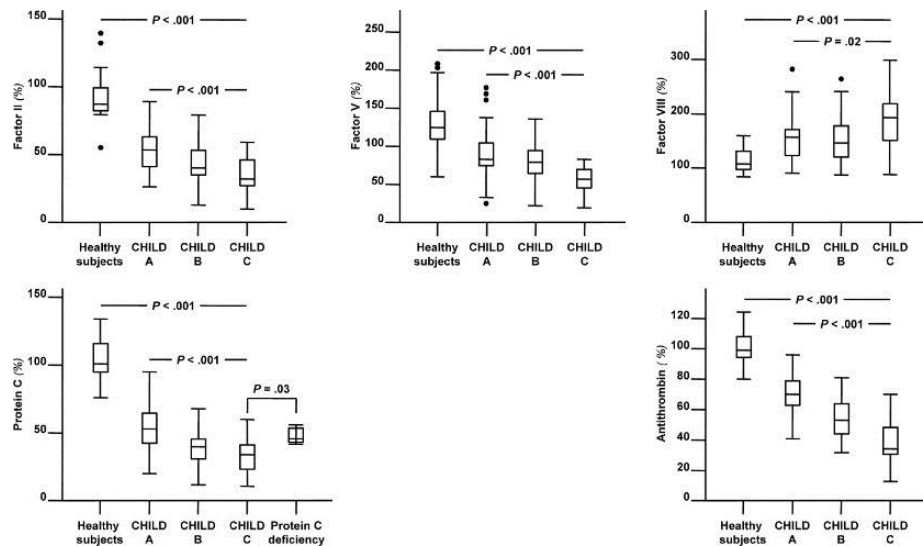


Fig. 1. Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for individual pro- and anti-coagulant factors for healthy subjects and patients with cirrhosis stratified according to classes of Child–Pugh (From Tripodi et al., 2009).

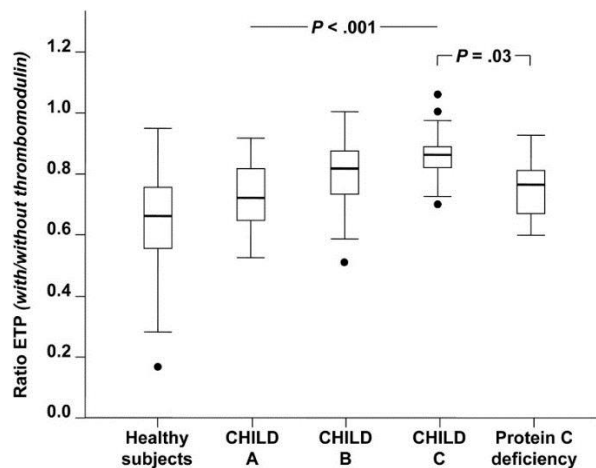


Fig. 2. Box plots of the distribution of values for ratios between thrombin generation assessed with/without thrombomodulin for healthy subjects, patients with cirrhosis (stratified according to classes of Child–Pugh), or with protein C congenital deficiency. Thrombin generation has been assessed as endogenous thrombin potential (ETP). From (Tripodi et al., 2009).

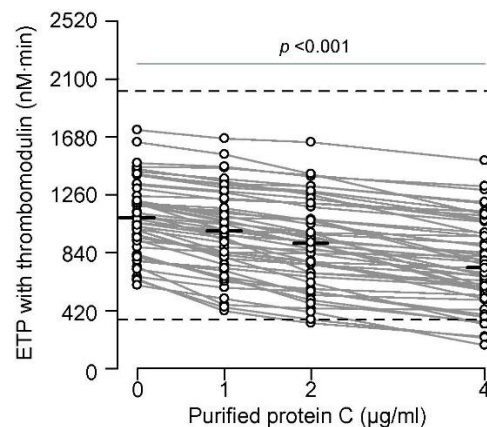


Fig. 3. Endogenous thrombin potential (ETP) measured in the presence of thrombomodulin before and after addition of purified human protein C to plasma from patients with cirrhosis. Horizontal bars represent median values. The horizontal lines represent the limits of the normal reference range derived from healthy subjects. From (Tripodi et al., 2013).

## Rebalanced Hemostasis in Chronic Liver Disease

Since the publication of the key paper in 2009 (Tripodi et al., 2009), a number of publications have explored various aspects of coagulation in chronic liver disease (reviewed in (Kujovich, 2015)). Hemostasis is achieved through the three major processes of primary hemostasis (mediated by platelets, von Willebrand factor and vessel wall interactions), secondary hemostasis (involving the cascade of plasma coagulation factors, leading to the generation of fibrin) and fibrinolysis. It is now appreciated that all three of these arms are changed in the presence of liver disease (Fig. 4).

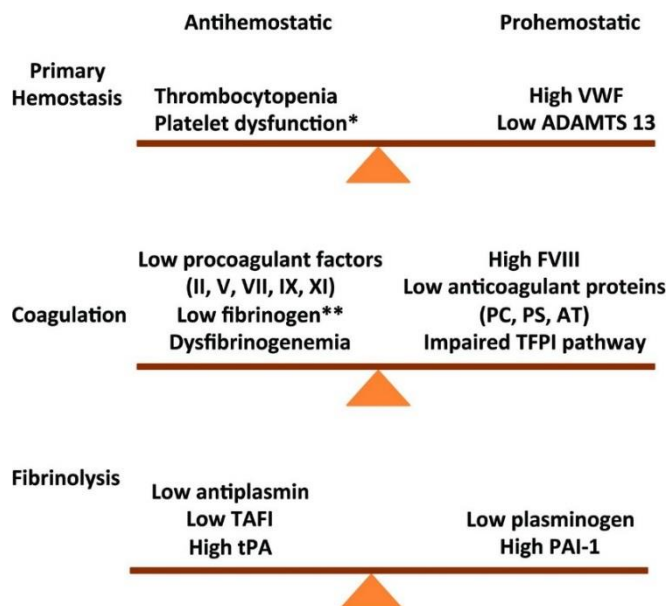


Fig. 4. Rebalanced hemostasis in chronic liver disease. Primary hemostasis: high VWF levels and low ADAMTS 13 levels counteract defects in primary hemostasis. Coagulation: reduced levels of procoagulant factors are balanced by a parallel decline in anticoagulant factors. Fibrinolysis: fibrinolysis is rebalanced by parallel changes in profibrinolytic and antifibrinolytic proteins. VWF indicates von Willebrand factor; ADAMTS 13, a disintegrin & metalloproteinase with thrombospondin type 1 motif 13; PC, protein C; PS, protein S; AT, antithrombin; \* does not occur consistently in chronic liver disease; and \*\*end-stage liver disease. From (Kujovich, 2015).

### Primary Hemostasis: The Role of Platelets and von Willebrand Factor

Platelet numbers are low in chronic liver disease for several reasons. Serum thrombopoietin levels are on average about one-third that of healthy controls (Pradella et al., 2011) because the liver is a major source of thrombopoietin. In addition, platelet turnover is increased as assessed by the immature platelet fraction. This is especially pronounced in patients with chronic hepatitis C, about a quarter of whom have measurable anti-platelet antibodies (Pradella et al., 2011). Splenic sequestration plays a role as cirrhosis becomes more advanced, but the correlation between spleen size and platelet count is imperfect. Platelet dysfunction does not occur consistently with chronic liver disease, but is often seen with the appearance of uremia. Von Willebrand factor, which is made in endothelial cells, is often highly elevated (Fig. 5), supporting platelet adhesion and normalizing primary hemostatic parameters (Fig. 6). (Lisman et al., 2006; Wannhoff et al., 2014). Elevated von Willebrand factor also stabilizes Factor VIII and contributes to high levels of Factor VIII in liver disease.

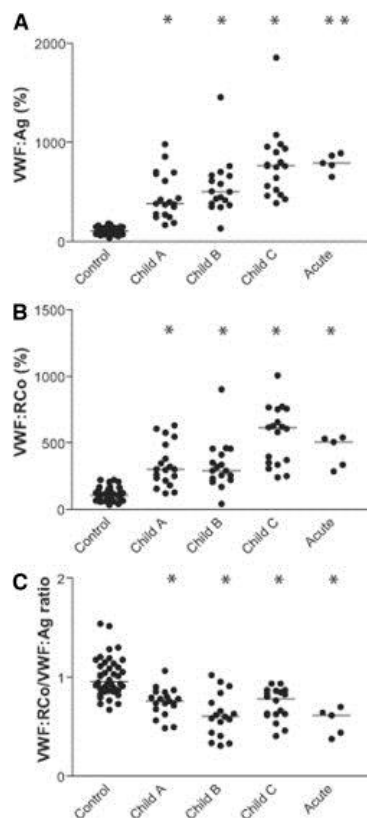


Fig. 5. VWF:Ag levels (A), VWF:RCo levels (B), and VWF:RCo/VWF:Ag ratio (C) in patients with Child A, B, and C cirrhosis and in patients with acute liver failure compared with VWF parameters as measured in healthy controls. VWF:Ag and VWF:RCo levels are expressed as a percentage of pooled normal plasma. Horizontal lines represent medians. \* $P < .001$ , \*\* $P < .01$ . VWF, von Willebrand factor. From (Lisman et al. 2006).

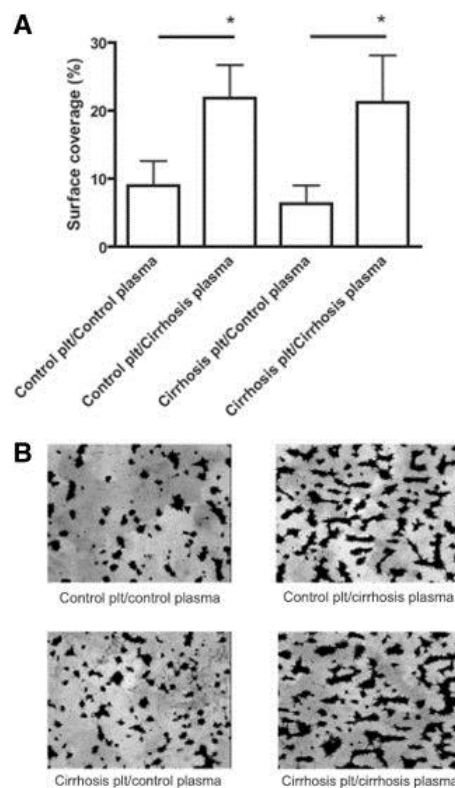


Fig. 6. Plasma from patients with cirrhosis better supports platelet adhesion than normal plasma. (A) Pooled plasma from patients with cirrhosis or pooled normal plasma was mixed with red cells and platelets isolated either from healthy volunteers or from patients with cirrhosis and perfused over a collagen-coated coverslip for 2 minutes. After May-Grünwald staining, surface coverage was determined. (B) Morphological appearance of the platelet thrombi on a collagen surface with reconstituted blood with patient or control plasma or platelets as indicated. From (Lisman et al. 2006).

## Secondary Hemostasis: Rebalanced Plasma Procoagulants and Anticoagulants

Secondary hemostasis occurs in plasma and results from the action of a cascade of activated procoagulants and anticoagulants (Fig. 7). Factors II, VI, VII, IX, X, and XI are all made in hepatocytes and decline during the progression of chronic liver disease. Fibrinogen is an acute phase reactant and levels are increased in chronic stable cirrhosis. In 50-80% of patients an abnormal fibrinogen is produced with increased sialic acid residues that impair polymerization. The anticoagulant proteins antithrombin, protein C and protein S fall to between 10 and 65% of normal, within the range of values seen in patients with inherited deficiencies (Tripodi et al., 2009; Tripodi et al., 2013). Tissue factor pathway inhibitor is increased in chronic liver disease but is functionally impaired by low levels of protein S. As discussed above, factor VIII levels are

increased due to increased synthesis (in endothelial cells), reduced clearance due to loss of liver receptors, and stabilization due to high levels of von Willebrand factor. (Kujovich, 2015).

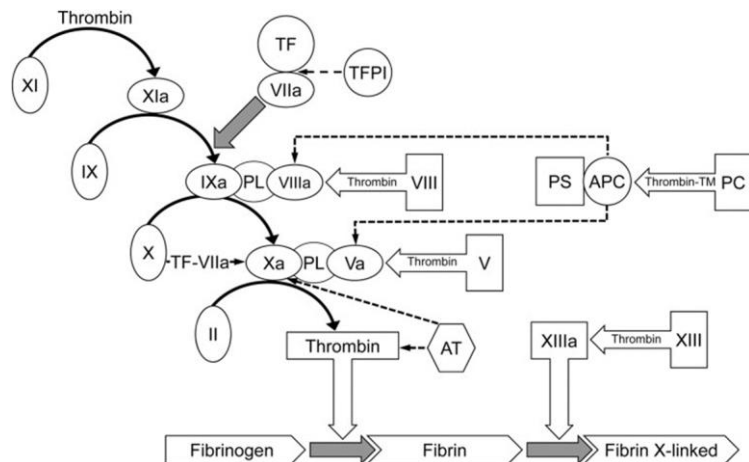


Fig. 7. Simplified scheme of the reactions leading to thrombin generation and inhibition. Roman numbers represent coagulation factors. Solid and broken arrows represent pro- and anti-coagulant drivers, respectively. TF, tissue factor; TFPI, tissue factor pathway inhibitor; PC, protein C; PS, protein S; APC, activated protein C; PL, negatively charged phospholipids on platelet membranes; AT, antithrombin. (From Tripodi, et al. 2009).

## Fibrinolysis

The fibrinolytic system consists of the degradation of fibrin by plasmin, which is generated from plasminogen by the action of tissue plasminogen activator (tPA) and opposed by the action of antiplasmin, PAI-1 and TAFI. Factor XIII serves to crosslink and stabilize fibrin. All of the pro- and antifibrinolytic proteins are synthesized by the liver except tPA and PAI-1, which are produced in endothelial cells. Antiplasmin and TAFI, made in liver cells, are generally low in chronic liver disease, and tPA is high, promoting fibrinolysis. Plasminogen is decreased and PAI-1 is increased, opposing fibrinolysis. The net effect is believed to be a rebalanced state (Fig. 4) (Kujovich, 2015). See (Leebeek, 2015) for a recent review.

## Tests for bleeding risk and their limitations

The PT/INR was developed to monitor warfarin anticoagulation, has long been used to prognosticate in liver disease and there is no reason to challenge its use for this purpose. However, because the PT/INR measures only the early phases of the procoagulant system (and because there is great inter-laboratory variation due to the “tissue thromboplastin” used to initiate the coagulation cascade), it does not reflect rebalanced anticoagulation and shows no correlation with bleeding risk in chronic liver disease. Extensive clinical data from the HALT-C trial illustrates this point (Seeff et al., 2010). The bleeding rate from 2740 liver biopsies was reported, and 16 cases (0.6%) of serious bleeding and no deaths were reported. While there was a higher rate of bleeding in patients with a platelet count less than 60,000 (still only 5%), the PT/INR was not predictive of bleeding risk. Twelve of the 16 instances of bleeding occurred at INRs of less than 1.0 to 1.2, and the remainder were at an INR of 1.3. No bleeding happened over an INR of 1.4. A second widely quoted study involving 852 procedures (including other procedures in addition to liver biopsy) reached a similar conclusion, and found that bleeding risk was unrelated to pre or post-platelet

procedure count, PT/INR or Child-Pugh classification. The only correlation was with the number of repeated procedures (Napolitano et al., 2017). For a recent review of six major studies reaching the same conclusion, see (Zakeri and Tsochatzis, 2017). Limitations of other tests to assess bleeding risk in liver disease are presented in Table 1.

**Table 1. Limitations of laboratory tests in patients with liver disease**

Laboratory test	Limitation
Platelet count	Threshold prediction of bleeding not defined
INR	Does not reflect platelet function Measures only procoagulant system Inter-laboratory variation in patients with CLD Not validated for CLD
PTT	Does not predict bleeding risk Measures only procoagulant system Usually doesn't reflect severity of liver disease Prolongation may be blunted by high FVIII levels in CLD
Procoagulant factor levels	Not as widely available Substantial laboratory variation No clear relationship to bleeding in CLD
Platelet aggregation	Only available in specialized coagulation labs Not calibrated for thrombocytopenia Must be performed within several hours of blood sampling
Thrombin generation test	Correlates poorly with bleeding Not widely available Too complicated for routine use Addition of thrombomodulin not standardized
Thromboelastography	Not widely available Most parameters not yet standardized Requires expertise to interpret tracings Not validated for predicting bleeding risk

INR indicates International Normalized Ratio; CLD, chronic liver disease; and PTT, partial thromboplastin time.

From (Kujovich 2015).

## **ROTEM (Rotational Thromboelastometry)**

ROTEM (or more generally thromboelastography or TEG) is a point of care device which presents the progress of whole blood “global” coagulation in real time and differs from traditional tests in that platelets and red blood cells are present. It is mainly used in surgery and trauma to guide blood product use, where it has been shown to reduce blood product utilization for intraoperative management in end-stage liver disease, but not improve outcome (Forkin et al., 2018). Whole blood is anticoagulated with citrate and the test started with addition of reagents. The viscoelasticity (“drag”) of the clot is presented in real-time, as the clot develops and dissolves. The clotting time (CT) is the time from the start of the assay to the beginning of clot formation. The MCF (maximum clot firmness) reflects the strength (“diameter”) of the clot.



Five tests are available (Fig. 8):

- INTEM: measures the intrinsic, or contact phase of coagulation, similar to the PTT
- EXTEM: measures the extrinsic phase, using tissue factor, like the PT/INR
- HEPTTEM: contains heparinase, eliminating the effect of heparin. Comparison of INTEM and HEPTTEM is used to detect the presence of heparin.
- FIBTEM: measures fibrin contribution to the clot. An EXTEM-based assay, in which platelets are inactivated by cytochalasin.
- APTEM: an EXTEM-based assay which uses aprotinin, an inhibitor of fibrinolysis. An improvement in the clot between the EXTEM and APTEM will detect severe fibrinolysis and can suggest the administration of antifibrinolytic agents.

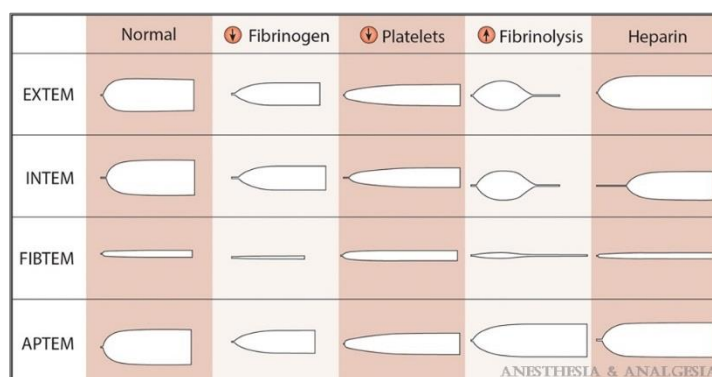


Fig. 8. Rotational thromboelastometry in normal and abnormal states. Typical tracings seen in the various ROTEM channels such as EXTEM, INTEM, FIBTEM, and APTEM. Normal viscoelastic testing is shown for comparison along with typical tracings for hypofibrinogenemia, thrombocytopenia, hyperfibrinolysis, and heparin effect. From (Forkin, et al. 2018).

The test may be useful in the detection of severe hyperfibrinolysis, which may occur in very advanced liver disease, and is the only widely available test for this purpose. It is considered less sensitive than the PT/INR to detect coagulation factor deficiencies. Like the PT/INR, its use has not been validated to assess bleeding risk in chronic liver disease, so its routine use for assessing bleeding risk cannot be recommended.

ROTEM and TEG are widely used in liver transplant surgery.

### Procedure Risk Assessment and Recommendations

Based on the literature, including studies cited above, the transfusion medicine service at UT Southwestern and Parkland have posted guidelines for pre-procedure bleeding risk assessment and management (<http://www.utsouthwestern.net/intranet/departments-centers/pathology/transfusion/pre-procedure-bleeding-risk-guideline-ir-utsw.pdf>). Interventional radiology procedures are grouped into different categories by level of invasiveness (Fig. 9). Note that recommended threshold laboratory values are different between cirrhotic and non-cirrhotic (normal) patients, with a maximum INR of 2.5 for patients with cirrhosis for all procedures. However, a highly prolonged INR and PTT should prompt testing for

fibrinogen level. It should be emphasized that personal and family history of bleeding is more predictive than laboratory testing. Platelet count thresholds of 30,000 for high-risk procedures and 20,000 for intermediate or low risk procedures are recommended, with the recognition that in the presence of splenomegaly, 80% of transfused platelets are sequestered in the spleen within 15 minutes of transfusion. It is advised that if platelets are to be transfused, one dose should be infused slowly for the duration of the procedure without checking platelet counts.

#### MINIMUM RECOMMENDED LABORATORY VALUES

		Antithrombotic Medications	Platelets	INR	PTT	Fibrinogen
Procedures with High risk of bleeding	Non Cirrhotic	Hold	50	1.6	32.5	100
	Cirrhotic	Hold	30	2.5	45	100
Procedures with intermediate risk of bleeding	Non Cirrhotic	Hold	50	2.0	32.5	100
	Cirrhotic	Hold	20	2.5	45	100
Procedures with Low risk of bleeding	Non Cirrhotic	Do not hold	50	2.0	32.5	100
	Cirrhotic	Do not hold	20	2.5	45	100

Fig. 9. UT Southwestern Vascular Interventional Radiology Guideline for Pre-procedure Bleeding Risk Assessment and Management.  
(<http://www.utsouthwestern.net/intranet/departments-centers/pathology/transfusion/pre-procedure-bleeding-risk-guideline-ir-utsw.pdf>).

Eltrombopag, a thrombopoietic agonist, has been studied for increasing platelet counts in patients with cirrhosis prior to procedures. The study was terminated early due to an unacceptable rate of thrombosis, especially portal vein thrombosis (Afdhal et al., 2012). A second generation drug, avatrombopag (Terrault et al., 2014), was studied in two phase III clinical trials (ADAPT1 and ADAPT2) and is undergoing FDA review, with results expected in May 2018.

#### Management of Acute Bleeding Episodes

Vasoconstrictor and endoscopic therapy and transfusion of packed red blood cells to a hemoglobin target of greater than 7 are the cornerstones of current therapy (Kujovich, 2015). Higher hemoglobin targets have been associated with poorer outcomes. It has been suggested that this is due to volume expansion, which may promote variceal bleeding. Platelet transfusion to values greater than 50,000 is often suggested, though rarely achieved in the presence of hypersplenism. Transfusion of cryoprecipitate is recommended to raise the fibrinogen to over 100 (various targets have been proposed elsewhere, 120 or even 150). Infusions of Factor VIIa, prothrombin complex concentrate (PCC), and desmopressin have shown no efficacy in clinical trials. Tranexamic acid is under study (HALT-IT) trial but results are not available. I have used oral aminocaproic acid in my own practice to reduce troublesome chronic mucosal bleeding in patients with end stage liver disease awaiting transplant, or for those who are not candidates for transplant, although it is not specifically FDA approved for this purpose.

It is important to recognize potential triggers of bleeding in chronic liver disease (Kujovich, 2015). Portal hypertension and local factors can be addressed by vessel ligation or shunt procedures (TIPS) to reduce portal pressures. Renal failure and bacterial infection are other potentially correctable factors. Renal failure is associated with platelet dysfunction, whereas bacteria have been shown to produce heparin-like substances that may prolong the PTT.

### **Hypercoagulability in Chronic Liver Disease**

So far, we have shown that the balance between pro- and anti-coagulation factors is not as stable in chronic liver disease as compared to normal subjects and that the risk of venous thromboembolism is two-fold higher. These findings should have implications for prevention and management of VTE. Accumulating evidence suggests that prevention and treatment of thrombosis may be safe and effective (Intagliata and Northup, 2015). Furthermore, early data suggests that hypercoagulability may even promote the development of fibrosis and hasten hepatic decompensation (Villa et al., 2012).

Low molecular weight heparin (LMWH) and warfarin are the most extensively studied agents in cirrhosis. LMWH has the advantage in that there are no recommendations for routine laboratory monitoring LMWH in cirrhosis, and in fact, anti-Xa assays to monitor the anticoagulant effect of LMWH can be misleading (due to the presence of antithrombin deficiency), leading to overdosing (Potze et al., 2013). Co-occurrence of renal insufficiency with chronic liver disease is also a potential contraindication. Vitamin K antagonists (warfarin) are problematic due to the baseline PT elevation in many patients and uncertainties regarding monitoring, often leading to under-anticoagulation. A specific INR calibrated to liver disease patients has been proposed (Tripodi et al., 2007), but is not ready for implementation.

Cirrhotic patients have been excluded from most clinical trials of the direct oral anticoagulants (DOACs) and clinical studies are needed before they can be recommended for routine use. However, small retrospective cohort studies suggest that they may be safe and effective in well-compensated cirrhosis patients (De Gottardi et al., 2017; Hum et al., 2017), despite concerns regarding liver metabolism. The pharmacokinetic profile of apixaban in liver disease may be more favorable as compared to rivaroxaban (Graff and Harder, 2013) and apixaban labeling recommends no dosage adjustment for Child-Pugh class A disease.

### *Venous thromboembolism (VTE) prophylaxis*

Hospitalized patients with cirrhosis are not inherently protected from deep venous thrombosis and pulmonary embolism (Northup et al., 2006). However, current guidelines do not address the role of prophylaxis in chronic liver disease patients, as neither safety nor efficacy have been clearly established. A systematic review found that it has not been possible to make recommendations based on published retrospective studies, which have been heterogeneous (Gomez Cuervo et al., 2013). It has been pointed out that very large numbers would be needed to achieve the statistical power for a clinical trial. However, it is recommended that routine thromboprophylaxis be considered for such patients if contraindications are absent (Intagliata and Northup, 2015).

### *Portal vein thrombosis prevention and treatment*

Portal vein thrombosis (PVT) is said to occur in between 2 and 16% of patients with cirrhosis, and can be acute and symptomatic, or silent and detected incidentally by imaging (ultrasound or CT or MRI). It may also be partial, complete, or extensive, with extension into the superior mesenteric venous (SMV) system. Studies pertinent to the topic of treatment are all retrospective and vary widely in their conclusions (reviewed in (Intagliata and Northup, 2015)). All patients with PVT should be screened for myeloproliferative disorder (MPD) (using the JAK2 mutation assay) as blood counts in MPD may be masked by splenic sequestration. Splenomegaly may be a feature of both cirrhosis and MPD, and patients with MPD may benefit from cytoreductive therapy. In addition, carefully selected patients should be considered for anticoagulant therapy, more strongly in acute PVT and those where the SMV system is threatened, and perhaps chronic PVT, although the evidence is not as strong. A recent meta-analysis of eight studies reporting on the use of LMWH or warfarin to treat cirrhosis with PVT (n=353, mean duration, 6 months, follow up, 2 years) showed improved rates of recanalization without a significant increase in bleeding (in fact, a lower risk for variceal bleeding for LMWH was observed) (Loffredo et al., 2017). An interesting and active area in clinical research based on animal studies is the role of chronic anticoagulation in slowing the rate of liver fibrosis in mild-moderate cirrhosis. A randomized controlled non-blinded study of Child-Pugh 7-10 subjects without a history of GI bleeding using enoxaparin 40 mg daily showed less progression to decompensation and even a survival advantage (Villa et al., 2012). It should be noted that these patients were highly selected (326/396 screened patients were excluded). Patients being considered for anticoagulation therapy should be screened for esophageal varices prior to initiation of anticoagulation (Intagliata and Northup, 2015).

### *Venous thromboembolism (VTE) treatment (not PVT)*

Unfortunately, no studies have examined the safety or efficacy of anticoagulants for VTE outside of PVT in chronic liver disease, and most prospective randomized studies have specifically excluded this population. Currently there are no guidelines outside of usual medical care. Clearly, such studies are needed. Choice of available agents are discussed in the paragraphs above.

### *Atrial fibrillation*

A very large retrospective analysis from the National Health Insurance Database of Taiwan (nearly 300,000 patients with atrial fibrillation, 10,000 with cirrhosis) (Kuo et al., 2017) concluded that warfarin use was associated with a reduced risk of ischemic stroke with only a slightly increased risk of intracranial hemorrhage (ICH). As ICH was much less frequent than ischemic stroke (by about 4-5 fold) there was a net clinical benefit for warfarin as compared to no treatment. Aspirin use was associated with higher risk of intracranial hemorrhage without a decrease in ischemic stroke, suggesting that aspirin is harmful (Fig. 10). A smaller retrospective study that stratified patients with regards to severity of liver disease suggested that warfarin may reduce clinical events in early (Child-Pugh A) liver disease but not in late (B or C) disease. Overall, these studies suggest that warfarin, but not aspirin, should be considered for stroke prevention in early stage cirrhosis. No data concerning DOACs in atrial fibrillation in liver disease is available. Prospective randomized trials are needed (Lee et al., 2015).

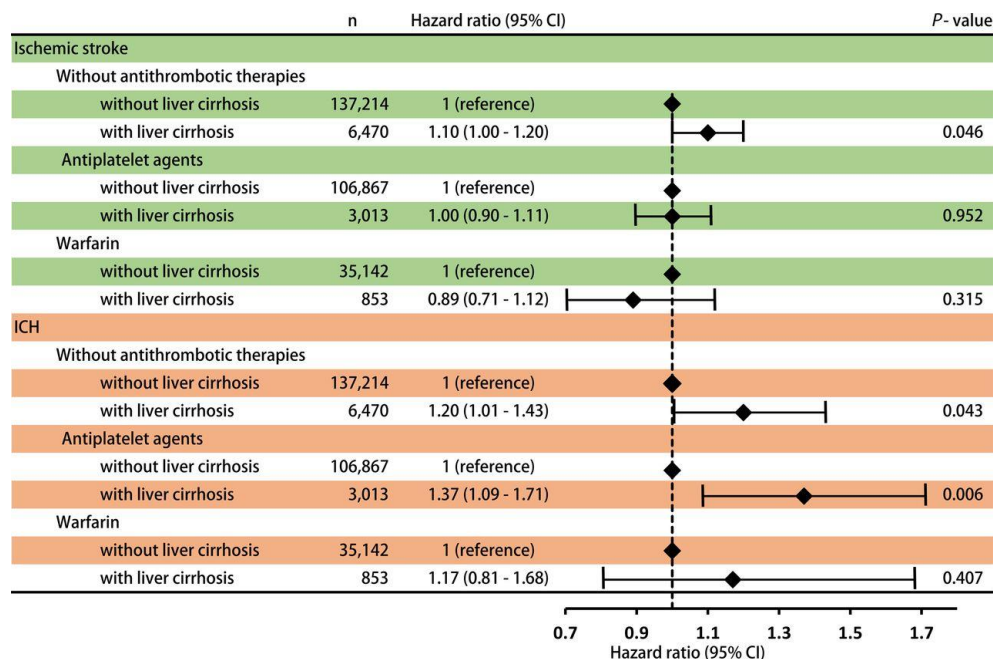


Fig. 10. Risk of ischemic stroke and ICH for AF patients with or without liver cirrhosis, stratified based on the strategies for stroke prevention. For patients who did not receive antithrombotic therapies, the risk of ischemic stroke and ICH was higher for AF patients with liver cirrhosis compared with those without. For patients treated with warfarin, the risk of ischemic stroke and ICH was similar between patients with or without liver cirrhosis. The hazard ratio was adjusted for age, sex, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, COPD, hyperlipidemia, malignancy, autoimmune diseases, end-stage renal disease, degree of urbanization, and income level. CI indicates confidence interval; ICH, intracranial hemorrhage. From (Kuo, et al. 2017).

## Summary and conclusion

Hemostasis in chronic liver disease is rebalanced due to changes in procoagulant, anticoagulant and fibrinolytic systems. This balance is fragile, leading to more clinically apparent thrombosis and bleeding. Current laboratory tests have limited utility for evaluating the coagulopathy of liver disease. The PT/INR, while useful for assessing the severity of liver disease, measures only procoagulant factors and is a poor predictor of bleeding risk. Fresh frozen plasma is not effective in shortening the PT/INR and its use should be minimized. Vitamin K and fibrinogen deficiencies can prolong the PT/INR and should be corrected, with vitamin K or infusion of cryoprecipitate. The threshold for safe platelet counts prior to procedures is unclear. A platelet count of 30 K is recommended prior to high-risk interventional radiology procedures but is rarely achievable in the presence of splenomegaly. Modifiable triggers of active bleeding in liver disease include portal hypertension, local vascular factors, renal failure, and bacterial infection. Patients with chronic liver disease are at increased risk of thrombosis but there is little guidance concerning optimal anticoagulation therapy. Hospitalized patients with cirrhosis should be considered for thromboprophylaxis in the absence of clinically apparent bleeding. Acute thrombosis in liver disease patients should be treated similarly to other patients and patients should be selected for secondary prevention of thrombosis on a case-by-case basis. The extent to which thrombosis contributes to liver fibrosis and the progression of cirrhosis is an interesting question which should be addressed in clinical trials.

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