Coagulation Disorders and Portal Vein Thrombosis in Cirrhosis

Stephen H. Caldwell, MD, Zachary Henry, MD, and Nicolas Intagliata, MD

University of Virginia
Charlottesville, VA

Key Concepts

• Despite prolongation of the prothrombin time, patients with cirrhosis often have decreased protein C and other changes leading to a rebalanced or even hypercoagulable state.
• Conventional tests, like INR, are not adequate measures of hemostasis in cirrhotic patients and other tests like Endogenous Thrombin Production (ETP) and Thromboelastography (TEG) need greater standardization and further translational study to better assess their clinical utility.
• Cirrhosis patients can develop hyperfibrinolysis and related bleeding complications. Diagnostic tests for this condition are not easily or widely available. A high index of suspicion is needed as anti-fibrinolytic agents such as Aminocaproic Acid may be beneficial.
• Portal vein thrombosis has an estimated annual incidence of 5-15% in patients with cirrhosis and has been associated with increased risk of decompensation, worse overall survival, and worse post-transplant outcomes.
• Anti-coagulation with vitamin K antagonists or low molecular weight heparin has been shown to be safe and should be considered in patients with portal vein thrombosis, whether acute or chronic, due to the favorable impact on transplant outcomes and overall survival. TIPS is also an option in selected cases and has the advantage of decreasing the risk of variceal bleeding.
• Prophylactic anti-coagulation with heparin products is safe and should be considered in hospitalized cirrhotic patients for the prevention of venous thromboembolism. It has also shown benefit in non-hospitalized compensated cirrhotic patients for prevention of portal vein thrombosis. In the latter setting, the benefit appears to extend beyond simply preventing portal vein thrombosis although further studies are needed to confirm these quite remarkable findings.

Recent studies have resulted in a paradigm shift in how cirrhotic coagulopathy is regarded. The concept of ‘auto-anticoagulation’ in cirrhosis is now discredited and the complexity of the bleeding and clotting diathesis associated with liver disease has become increasingly apparent and clinically relevant in surprising, paradoxical, and often perplexing ways.

Laboratory Assessment of the Clotting Cascade in Cirrhosis

As measured by more physiological laboratory techniques, it is now evident that stable cirrhosis is hematologically characterized by relatively preserved hemostatic mechanisms. Cirrhosis may even be associated with a hypercoagulable state despite prolongation of the prothrombin time (PT) and INR (international normalized ratio) and/or thrombocytopenia. Key laboratory methods include the thrombin generation assay (endogenous
thrombin production or ETP). This test measures the capacity of blood to produce thrombin or activated factor II (which then converts fibrinogen to fibrin clot). Global clotting assays, like thromboelastography (TEG, Rotem, Sonorheometry), measure the physical properties of actual clot formation and subsequent dissolution by physiological fibrinolysis. Prolongation of the PT/INR indicates decreased liver synthesis of pro-coagulant factors, but these changes are offset by impaired hepatic synthesis of anti-coagulant factors such as protein C, S and antithrombin (AT) and other changes in relevant factors synthesized by the vascular endothelial cells.

**Protein C and Thrombomodulin**

Impaired hepatic synthesis of protein C combined with normal levels of endothelial-derived thrombomodulin (a protein C co-factor – see below) and increased levels of endothelial-derived factor VIII and von Willebrand factor, lead to enhanced thrombin (activated factor II) production and enhanced aspects of platelet function such as adhesion.1,2,3 Thrombomodulin (TM) has played a key role in recent advances in laboratory testing. TM is a transmembrane glycoprotein which exists mainly in the endothelium (less so in a soluble form) which promotes protein C activation. Its use in thrombin generation assays permits more physiological study of the pro- and anti-coagulant systems in cirrhosis. Normally, activated protein C (APC) together with TM and additional co-factors including protein S and negatively charged phospholipids, inactivates factors V and VIII thereby limiting thrombin production (thus promoting anticoagulation).

Blood sample testing with the addition of a physiological amount of TM reveals that when a normal amount of protein C is present, thrombin production is limited by the presence of APC. On the other hand, in cirrhosis, low levels of hepatic-derived protein C and high levels of endothelial-derived factor VIII augment thrombin production, which can then convert fibrinogen to fibrin clot. Notably, past series have shown fibrinogen levels are often preserved or only mildly decreased in cirrhosis.4 These compensatory changes thus offset diminished hepatic synthesis of pro-coagulant factors, preserve the hemostatic pathway of clot formation, and can result in a net hypercoagulable state.5

As a result, hemostatic mechanisms in stable cirrhosis are best seen as essentially rebalanced albeit in a fragile state that can be tilted in either direction depending on complex exogenous factors.6 Bleeding problems are dominant in day-to-day practice, especially among hospitalized patients. However, thrombotic processes can dominate and may ultimately propel the compensated cirrhotic liver into a state of atrophy and failure.7,8 Bleeding is favored by a number of common superimposed conditions including infection (via release of endogenous heparinoids from endothelial cells) and renal failure (by dysfunctional uremic platelets).9,10 In addition, a state of hyperfibrinolysis may occur (see below) characterized by premature clot dissolution. Pressure driven systems, such as portal collaterals, may also complicate the disorder and warrant careful consideration of the ill-effects of excessive volume expansion on portal pressure.11 Thrombotic issues may dominate as a result of changes in the over-all balance of pro- and anti-coagulant pathways and especially by stasis of blood flow in which latent hypercoagulability may dominate.12 In addition, the production of microparticles (phospholipid vesicles) by the sick liver may cause a dynamic and very little explored stimulant of coagulation.13,14

**The Precarious Balance: Accelerated Intravascular Coagulation and Fibrinolysis (AICF)?**

Although the term ‘DIC’ is sometimes used loosely to describe the coagulopathy of liver disease especially in decompensated patients, the disorder often lacks features of classical DIC such as rapidly declining platelets and fibrinogen and decreased FVIII. The term ‘AICF’ has been proposed as a more accurate descriptor of cirrhotic coagulopathy characterized by low but usually stable platelet levels, mildly decreased or normal fibrinogen, decreased pro- and anti-coagulant factors, increased Factor VIII and von Willebrand factor, increased clot degradation products and increased fibrinolytic (clot dissolution) capacity.15,16

**Hyperfibrinolysis**

Increased fibrinolytic capacity is one of the earliest observations regarding coagulopathy in liver disease as evident from Dr EW Goodpasture’s 1914 study describing the increased fibrinolytic capacity of blood in liver disease. Sixty years later, Boks et al demonstrated the difficulty in predicting bleeding in both acute and decompensated chronic liver disease based on conventional measures of hemostasis among hospitalized patients.4 In that study, mucosal-type (non-variceal) bleeding could only be predicted by factoring in a measure of fibrinolysis or clot dissolution. The clinical syndrome of hyperfibrinolysis is perhaps most evident in the decompensated cirrhotic where it is characterized by mucosal and puncture wound oozing.
and, sometimes delayed, post-procedure bleeding. It is estimated to be clinically apparent in around 5-10% of decompensated cirrhosis.17 The mechanism is uncertain but abnormal metabolism of TAFI (Thrombin Activatable Fibrinolysis Inhibitor) has been implicated19 as has the presence of ascites. Expressed as 'Global Fibrinolytic Capacity', a step-wise increase is evident in progressively more severe liver disease.19 The clinical importance of recognizing the condition lies in the potential role of anti-fibrinolytics, such as Amicar (aminocaproic acid), to slow clot dissolution. It is perhaps worth mentioning also that most body cavities appear to have fibrinolytic capacity including the oral cavity, bladder and peritoneal cavity. Thromboelastography (TEG – see below) is probably the most convincing laboratory test to confirm the diagnosis of hyperfibrinolysis but its limited availability and variation in performance necessitate the continued reliance on clinical suspicion.

**Laboratory Studies**

As discussed above, advances in clinical laboratory testing have led the way to a more practical understanding of the hemostatic mechanisms in clinical liver disease.12 As a result, there has been increasing recognition of the conventional INR in cirrhosis as a narrowly focused assay with significant inter-laboratory variation (depending, as shown initially by J Trotter, on commercially available thromboplastins). However, many of the recent studies, especially those involving the ETP test (endogenous thrombin production) have been performed in stable out-patients without strong clinical/translational studies in decompensated in-patients. Thromboelastography (TEG) has also re-emerged as a leading candidate for a global measure in cirrhosis. Indeed, there is extensive published experience and precedent in defining hypercoagulability based on measured parameters of the TEG such as rate of clot formation and maximal clot strength.20 Despite this situation, it is also apparent that there is significant inter-center variation in nuances of the test and different types of elastography appear to vary in their performance and ability to detect hyperfibrinolysis (unpublished experience). Clearly, clinically relevant translational studies are needed to refine this approach and understand the strengths and limitations of various approaches. At our center, we have come to rely more on platelet levels and fibrinogen levels as stop gap measures of hemostasis and much less on the potentially misleading INR while we anxiously await the results of ongoing studies.12

**DVT in Cirrhosis**

Based on the foregoing discussion, it is not surprising that hospitalized cirrhosis patients are at risk for peripheral deep venous thrombosis with an estimated incidence of around 1-2%.21,22 Conventional DVT prophylaxis is felt to be safe in such patients in the absence of bleeding although efficacy measures remain uncertain due to changes in for example heparin co-factors (liver-derived AT) which have not been fully investigated and may cause resistance to heparin activity.23

**Portal Vein Thrombosis (PVT) in Cirrhosis—Clinical Significance**

Among cirrhotic patients without HCC (which increases the risk), PVT is estimated to develop in 5% to 15% of patients annually with a prevalence of 25% or more.24 Assessment of the existing literature is complicated by existence of only a few prospective studies. In addition, the clinical spectrum of the disorder is broad and ranges from partial to occlusive PVT, overtly symptomatic to subclinical, localized or extensive, acute versus chronic with cavernous transformation (cavernoma) and concurrent presence or absence of variable risk factors like Factor V Leiden and Prothrombin mutation (which are infrequent but potentially significant prothrombotic (thrombophilic) factors in these patients and can occur in about 10-15% of cases).25 However, slow portal vein blood flow (<15 cm/s) appears to be the most significant risk for PVT.26 The situation warrants future consideration of beta blocker effects which are known to decrease portal flow. It is also interesting to speculate on the potential role of liver derived pro-coagulant microparticles (see above). The association of PVT in cirrhosis with smaller liver size, ascites and hydrothorax, recurrent variceal bleeding, increased Child-Pugh/MELD scores and especially the effect on survival convincingly argue for its clinical significance.27,28 Moreover, PVT has a significant impact on the technical aspects of transplant surgery and a complicated but detrimental effect on outcomes: PVT pre-transplant shifts the survival benefit of transplant such that the net benefit of transplant on survival is evident only at higher pre-transplant MELD.29

**Clinical Evaluation and Therapy in Cirrhotic PVT**

The discovery of PVT in a cirrhosis patient, usually detected first by screening ultrasound, should be first confirmed by cross-sectional venous phase imaging with CT or MRI. When confirmed, a hypercoagulable workup including testing for FV Leiden, prothrombin 20210, and
MTHFR (methyleneetetrahydrofolate reductase) mutations in order to assess fixed thrombotic risks may help to guide long-term therapy with anti-coagulants. The utility of individual factor levels (Protein C, S and AT) in this setting is less clear as their interpretation in cirrhosis is challenging although this clearly requires further investigation. Early endoscopy should be undertaken with band ligation if significant varices are evident (unless perhaps if TIPS portal decompression is planned).

With the increasing awareness of PVT effects on morbidity, survival and transplantation, efforts to reverse the process with systemic anti-coagulation are increasingly accepted. Anti-coagulation with coumadin or low molecular weight heparin results in recanalization in 40-60% of patients (compared to very infrequent spontaneous recanalization) and appears to have a favorable impact on transplant outcomes. Close clinical follow-up in these patients is challenging but essential. The potential role of newer anti-coagulants such as factor Xa inhibitors warrants consideration, but also requires caution in listed patients due to issues of reversibility. Although there are only a few studies, TIPS (usually along with post-procedure anti-coagulation) is a viable option in these patients even with occlusive PVT provided intrahepatic portal branches can be visualized. This approach has the advantage of offering varices decompression but carries technical challenges in some patients and increased risk of hepatic decompensation with higher MELD scores.

Should We Anti-coagulate Stable Cirrhosis Without PVT?

Based on the problems associated with the occurrence of PVT and the pro-coagulant changes of cirrhosis, prospective, prophylactic anti-coagulant studies have been undertaken aimed primarily at preventing PVT with surprising results. In a study of enoxaparin in patients with PVT presenting with esophageal variceal bleeding (anti-coagulation started after varices eradication with banding), Amitrano et al noted no benefit in terms of variceal re-bleeding but a surprising improvement in survival in the treated group. These results have been remarkably advanced in a subsequent provocative, prospective, controlled, and partially blinded trial by Villa et al. Cirrhosis patients without PVT were randomized to prophylactic dosing of enoxaparin (34 versus no treatment (36) for 48 weeks with an additional year of follow-up consisting of q3mos US and q6mos CT. The divergence of the curves for not only PVT but also for episodes of decompensation and actuarial survival is impressive. The differences were attributed in part to decreased gut microbial translocation and improved gut perfusion. However, a possible intrahepatic mechanism is suggested by other work. This includes the proposed role of intrahepatic microvascular thrombosis in parenchymal extinction put forward by Wanless et al as a mechanism of liver atrophy in cirrhosis, work by Anstee and Thursz et al showing thrombin to activate fibrosis pathways in stellate cells via the PAR-1 receptor (PAR: protease activated receptor) and unpublished work by Y Ikura et al showing evidence of intra-hepatic activated platelets in advanced cirrhosis.

Table: Key considerations in newly recognized Portal Vein Thrombosis in cirrhosis

1. Recall that slow portal flow (<15 cm/s) is one of the major risks for PVT
2. Exclude non-cirrhotic PVT (not considered here)
3. Confirm PVT and assess extent with cross sectional imaging
   - Partial PVT or occlusive
   - Are intra-hepatic portal branches evident?
   - Is there extension into the mesenteric system?
   - Are large porto-systemic collaterals present which promote slow portal flow?
4. Are symptoms evident such as ascites, variceal bleeding, abdominal pain or overall deterioration (although often silent, about 1/2 or more of patients experience some symptoms)
5. Assess genetic thrombophilic factors which may affect the duration of subsequent therapy: Factor V Leiden, Prothrombin mutation, MTHFR (individual factor levels can also be measured but are difficult to interpret in cirrhosis, anti-cardiolipins may also be measured but their relevance in this setting is uncertain)
6. Assess for varices and undertake banding if high risk unless TIPS is planned
7. Consider TIPS (and thrombectomy) in selected cases if portal vein branches are evident and in the absence of cavernous transformation
8. Anti-coagulation therapy: risk-benefit remains to be established but is probably most-favorable at this time in transplant candidates. However, there is emerging data on the overall favorable effects on hepatic function of prophylactic anticoagulation in stable cirrhosis so increasing potential role in PVT
   - Coumadin: studied in a number of series, target INR generally 2-3, obvious challenges in monitoring and dosing adjustments, generally available and inexpensive
   - Low molecular weight heparin (LMWR): optimal dosing and possible resistance (due to low anti-thrombin) have not been well studied. Appears effective in prophylactic dosing (see paper by Villa et al). Costs may be a problem and inconvenience of injection is a drawback
   - Newer agents (oral Xa inhibitors) are expected to undergo study
These complementary pathways need to be revisited in future studies of anti-coagulation therapy in cirrhosis.

Conclusion

The 'coagulopathy of cirrhosis' is extraordinarily dynamic and complex. Our understanding of this condition has dramatically evolved over the last decade. Studies now show that clinicians must look beyond the notion that conventional laboratory tests accurately convey bleeding or clotting risk in these patients. The liver produces nearly all of the proteins needed to form clots at sites of damaged vessel walls (coagulation/hemostasis), but also produces the majority of proteins that govern this cascade, by providing inhibitory and fibrinolytic control (anticoagulation). When this balance is disturbed, pathology in the form of bleeding or thrombosis is clinically observed. In cirrhosis, the imbalance is mitigated by compensatory mechanisms although consequences of portal hypertension lead to disruption of this tenuous balance. As our understanding of this process evolves, developing laboratory tests that allow the clinician to better predict the patient's relative risk to bleed or clot is an essential goal to guide therapy. Another very interesting area of research in this field includes examining the role of microparticles in coagulation and fibrinolysis in cirrhosis patients. New oral anticoagulation medications remain to be explored in cirrhosis patients but hold promise as a means of preventing deterioration of the injured organ. As our understanding of the complex hemostatic state of cirrhosis continues to advance, our ability to prevent and predict clinical sequelae of bleeding and clotting will undoubtedly improve.

References

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