Coagulopathy in cirrhosis

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Coagulation in cirrhosis is often profoundly deranged. The following discussion will attempt to explore various components of coagulation, but keep in mind that these work together synergistically. Thus, considering each in isolation is an oversimplification of reality. For example, in vivo it is conceivable that elevated fibrinogen function might compensate for reduced platelet function.

Coagulation physiology in cirrhosis

Primary hemostasis – von Willebrand factor and platelet function

Secondary hemostasis – enzymatic coagulation

Clinical pearls

Fibrinolytic system & accelerated intravascular coagulation and fibrinolysis (AICF)

Vitamin K challenge

Relationship of infection with hemorrhage

Approach to common problems

Coagulation management during active hemorrhage

Coagulation management prior to a planned procedure

DVT prophylaxis

Podcast

Questions & discussion

Pitfalls

PDF of this chapter

Coagulopathy in cirrhosis

vWF and platelet function

Enzymatic coagulation
thrombocytopenia is common in liver disease

- Thrombocytopenia is seen in most patients with cirrhosis, but it's rarely severe (e.g. <50,000/uL). ([32090357](https://pubmed.ncbi.nlm.nih.gov/32090357/))
- Causes of thrombocytopenia include:
  - Splenic sequestration and destruction.
  - Reduced production due to impaired hepatic synthesis of thrombopoietin (which normally stimulates the marrow to produce platelets).
  - Bone marrow suppression, due to alcoholism or hepatitis C virus infection.

platelet number may be a poor predictor of platelet function

- A complete blood count measures platelet numbers, but not their function. Unfortunately, platelet count doesn't account for other factors which may affect platelet function.
- Factors which may enhance platelet function in cirrhosis:
  - i) Increased levels of platelet adhesion factor.
  - ii) Increased levels of von Willebrand factor (which is produced by endothelial cells and often elevated in cirrhosis). von Willebrand factor is involved in formation of cross-links between platelets, promoting formation of a platelet plug.
- Factors which may impair platelet function:
  - Uremic platelet dysfunction (e.g., hepatorenal syndrome).
  - Sepsis or endotoxemia, due to bacterial translocation.
- Overall, patients with cirrhosis often have relatively normal platelet function, with thrombocytopenia being off-set by elevated levels of von Willebrand factor.

secondary hemostasis – enzymatic coagulation

enzymatic coagulation may be reduced, normal, or elevated

- Enzymatic coagulation refers to the ability of clotting factors to initiate the activation of fibrinogen.
- Enzymatic coagulation is traditionally measured by the INR and PTT. In a thromboelastogram assay, enzymatic coagulation is measured by the R-time.
- Patients with liver disease may be have reduced, normal, or increased enzymatic coagulation:
  - Most clotting factors are synthesized by the liver (e.g., fibrinogen, thrombin = factor II, and factors V, VII, IX, X, and XI). Reduction in these clotting factors tends to cause reduced enzymatic coagulation.
  - Naturally occurring anticoagulants (e.g. protein C, protein S, and antithrombin III) are also synthesized by the liver. Deficiency of these tends to augment enzymatic coagulation.
  - Factor VIII is produced by endothelial cells and tends to be upregulated in cirrhosis, augmenting coagulation.
  - The precise balance is unpredictable. Most patients with cirrhosis tend to have normal or increased enzymatic coagulation.

the significance of INR in liver failure

- The INR measures the function of a limited number of clotting factors (fibrinogen, II, VII, IX, X). The INR is unable to measure the function of naturally occurring anticoagulants (e.g., protein C, protein S). Thus, the INR is unable to evaluate the overall balance of procoagulants vs. anticoagulants.
- An elevated INR reveals nothing about the overall state of enzymatic coagulation.
  - Many patients with INR elevation have normal enzymatic coagulation, due to a balanced reduction of both clotting factors and anticoagulant proteins (this is termed "rebalanced coagulation").
  - Among patients with cirrhosis and elevated INR, some may have reduced enzymatic coagulation, but more often they will be hyper-coagulable.
- So, what is the meaning of the INR in cirrhosis?
  - The INR doesn't predict postprocedure bleeding, nor does it illuminate the state of enzymatic coagulation.
  - The INR does reflect hepatic synthetic failure – so it is a useful prognostic factor regarding the severity of the liver disease. This assumes, however, that the patient hasn't recently received fresh frozen plasma or warfarin – in which case the INR won't reliably
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reflect hepatic synthetic function.

**the use of thromboelastography in liver failure**

- Thromboelastography seems to be better than the INR to determine the overall balance of enzymatic coagulation, because it is able to evaluate both clotting factors and anticoagulants.
- Most patients with cirrhosis will have an elevated INR with a normal R-time (indicating normal enzymatic coagulation) or a reduced R-time (indicating augmented enzymatic coagulation).
- RCTs have demonstrated that thromboelastography may reduce blood product utilization, without affecting the risk of bleeding.

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**fibrinolytic system & accelerated intravascular coagulation and fibrinolysis (AICF)**

**importance of fibrinolysis**

- Fibrinolysis is the process of clot *degradation*. Normally, there is a fine balance between profibrinolytic factors versus antifibrinolytic factors. Imbalances may lead to hemorrhage or clotting.
- Fibrinolysis is difficult to evaluate with laboratory tests, causing it to often be ignored.

**cirrhosis tends to cause hyperfibrinolysis**

- Excessive fibrinolysis causes rapid clot breakdown and depletion of fibrinogen. Cirrhosis causes this for a few reasons, most notably:
  - (1) Normally, the endothelium releases tiny amounts of tissue plasminogen activator (tPA), which is subsequently cleared by the liver. Failure of the liver to metabolize endogenous tPA leads to increasing tPA levels. Patients may behave as if they are on a continuous tPA infusion!
  - (2) Decreased hepatic production of antifibrinolytic proteins may further tip the balance towards fibrinolysis (e.g., decreased levels of alpha 2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI))

**accelerated intravascular coagulation and fibrinolysis (AICF): basics**

- AICF refers to a clinically relevant state of hyperfibrinolysis resulting from cirrhosis. It has some similarities to disseminated intravascular coagulation (DIC), but it's not the same thing.
  - In DIC, the primary problem is excessive activation of coagulation (with excessive thrombin generation).
  - In accelerated intravascular coagulation and fibrinolysis, the primary problem is excessive fibrinolysis.
- AICF is relatively uncommon, occurring predominantly in advanced or decompensated cirrhosis.
- Since AICF is uncommon and we lack simple tests of hyperfibrinolysis, AICF is often missed. Failure to diagnose AICF may lead to intractable hemorrhage that doesn't respond to usual treatment.

(https://emcrit.org/ibcc/cirrhosis/attachment/aicfsum/)

https://emcrit.org/ibcc/cirrhosis/
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Clinical manifestations of acute intravascular coagulation and fibrinolysis (AICF)

- Clinical manifestations may include:
  - Intractable delayed bleeding following procedures or trauma (e.g., oozing from line sites).
  - Spontaneous bleeding (e.g., intramuscular hematoma, mucocutaneous bleeding).
  - Persistent gastrointestinal bleeding due to portal gastropathy.
- A hallmark manifestation of AICF is gradual, persistent bleeding that fails to respond to usual therapy. Usually these patients don't have a severe anatomic lesion as the cause of bleeding – so bleeding is not immediately life-threatening. For example, consider ACIF in a patient with portal gastropathy who lingers in the ICU with persistent ongoing blood loss day after day, despite usual treatments.

Diagnosis of accelerated intravascular coagulation and fibrinolysis (AICF)

- Challenges to establishing the diagnosis of AICF:
  - (1) There are no precise diagnostic criteria for AICF. Some studies suggest that hyperfibrinolysis occurs in ~30% of patients with cirrhosis, but in most cases this is mild and not clinically relevant. (26049070)
  - (2) There is no widely available lab test which accurately detects fibrinolysis. Thromboelastography (TEG) is relatively insensitive to hyperfibrinolysis, because tPA rapidly becomes inactivated in vitro. (26049070) Therefore, a normal LY-30 doesn't exclude hyperfibrinolysis. However, any elevation of the LY-30 may support the presence of hyperfibrinolysis.
  - (3) Patients who are bleeding often receive a potpourri of blood products. This may obscure their underlying coagulation status.
- Nonetheless, AICF may be diagnosed on the basis of recognizing the following pattern of clinical and laboratory findings:
  - Clinical findings:
    - Patients generally have advanced cirrhosis.
    - Intractable bleeding which fails to respond to usual therapy.
  - Laboratory findings
    - D-dimer levels are profoundly elevated.
    - Fibrinogen levels are unusually low compared to most patients with cirrhosis.
    - Fibrinogen levels respond initially following supplementation, but subsequently fibrinogen levels continually drift downwards and require frequent repletion.
- AICF and DIC share several similarities. Unlike in DIC, patients with AICF will typically have reasonably stable platelet counts and elevated levels of factor VIII (values which would be reduced in DIC). (21475134)

Treatment of accelerated intravascular coagulation and fibrinolysis (AICF)

- (1) Restoration of fibrinogen levels (e.g., using cryoprecipitate or fibrinogen concentrate transfusion).
  - For intractable bleeding, targeting a relatively higher fibrinogen level (e.g., >150-200 mg/dL) could be helpful. Unfortunately, there is no high-level evidence regarding the optimal fibrinogen target.
  - Combination with an ongoing infusion of tranexamic acid is generally required to maintain adequate fibrinogen levels over time.
- (2) Tranexamic acid (a fibrinolysis inhibitor) is required to maintain adequate fibrinogen levels and to prevent excess clot degradation.
  - A starting dose may be 1 gram IV, followed by a continuous infusion of one gram over 8 hours repeatedly (i.e., 125 mg/hr infusion). (30986390) This is the standard dosing utilized in traumatology studies, such as the CRASH trials.
  - The optimal dose is unclear. In refractory cases, higher doses of tranexamic acid may be required (e.g., 200 mg/hour infusion). (31294331) Risk of seizure may increase at higher doses, so avoid using high-dose tranexamic acid in combination with other medications that reduce seizure threshold.
  - After bleeding has resolved, IV tranexamic acid may be converted to oral tranexamic acid (e.g., 1300 mg PO q6hr).

Vitamin K challenge – diagnostic & therapeutic

- Patients with cirrhosis may have vitamin K deficiency, due to the following:
  - Malabsorption due to cholestatic liver disease (bile salts are required to absorb dietary vitamin K)
  - Malnutrition
  - Antibiotic use
  - Prior use of vitamin K antagonists (e.g., warfarin)

https://emcrit.org/ibcc/cirrhosis/
Both vitamin K deficiency and hepatic dysfunction can cause prolongation of INR and aPTT.

Intravenous vitamin K may be given as a diagnostic/therapeutic challenge, if it is unclear whether INR prolongation is due to vitamin K deficiency:
- 10 mg IV vitamin K is infused over 30-60 minutes. Coagulation studies are obtained the following day.
- If INR improves, this is diagnostic of vitamin K deficiency. Any residual INR elevation may be attributed to hepatic dysfunction.
- Vitamin K administration may be helpful prognostically (to ensure that INR elevation actually is an accurate reflection of liver function).
- IV Vitamin K challenge is a useful approach to INR elevation in other situations as well (e.g., malnourished ICU patients can develop vitamin K deficiency).

**relationship of infection & hemorrhage**

**relationship between bleeding and infection in cirrhosis**

- In normal patients, infection often leads to a hypercoagulable state. However, in cirrhosis, reduced coagulation factors make the balance between coagulation and anticoagulation fragile.
- Patients with cirrhosis often develop coagulopathy and clinical hemorrhage when they are infected. This may involve the release of endogenous heparinoids from the vascular endothelium, which have an anticoagulant effect. ([27974342](https://pubmed.ncbi.nlm.nih.gov/27974342/))

**clinical significance**

- In some patients with cirrhosis, gastrointestinal hemorrhage may be the initial manifestation of an occult infection. Thus, patients with cirrhosis and GI hemorrhage should be routinely evaluated for spontaneous bacterial peritonitis if they have ascites.
- RCTs have shown that patients with cirrhosis and gastrointestinal hemorrhage benefit substantially from ceftriaxone. It's conceivable that the ceftriaxone is beneficial for these patients because it is treating an occult infectious process that triggered the gastrointestinal hemorrhage (rather than necessarily "prophylaxing" against the development of a subsequent infection).

**coagulation management during active hemorrhage**

**evaluation**

- Complete blood count
- Fibrinogen level
- Thromboelastography (TEG) ideally, or INR if unavailable

**platelet transfusion**

- This may be considered for active bleeding with platelet count <50,000/uL.
- Platelet transfusion often causes only transient increase in platelet count.

**fibrinogen supplementation**

- This may be considered for active bleeding with fibrinogen level below ~150 mg/dL (sources vary regarding targets, ranging between >100 to >200 mg/dL). ([30855324](https://pubmed.ncbi.nlm.nih.gov/30855324/))
- For patients with thrombocytopenia, which is difficult to treat, it may be reasonable to target a somewhat higher fibrinogen level than usual. Platelets work synergistically with fibrinogen, so higher levels of fibrinogen may compensate to a certain degree for thrombocytopenia.
- Either cryoprecipitate or fibrinogen concentrates may be used, depending on availability.

**Fresh Frozen Plasma (FFP)**

- Fresh frozen plasma is generally overutilized in bleeding patients with cirrhosis. Fresh frozen plasma is unlikely to help most patients, because most patients don't have true enzymatic coagulopathy. Thus, several studies have found that among most patients with cirrhosis, administration of FFP fails to augment coagulation. ([30986390](https://pubmed.ncbi.nlm.nih.gov/30986390/), 31661175 [30855324](https://pubmed.ncbi.nlm.nih.gov/30855324/)) FFP will make the INR lower – but it won't affect *in vivo* clot formation.
For a patient who is actively bleeding and has impaired enzymatic coagulation on thromboelastography (e.g., a substantially prolonged R-time), fresh frozen plasma is a rational therapy. However, finding true enzymatic hypocoagulation is uncommon in the absence of other causes (e.g., warfarin use, massive transfusion).

If thromboelastography isn’t available, fresh frozen plasma could be contemplated for management of active bleeding with a **profoundly** prolonged INR. However, administration of FFP should be tempered by the sobering understanding that it will make laboratory values look better, yet is unlikely to help the patient. When in doubt, fibrinogen or platelet supplementation is generally more likely to improve coagulation, when compared to fresh frozen plasma.

Four-factor prothrombin complex concentrates (PCC) is another option to replace coagulation factors. The main advantage of PCC is that it involves less volume administration, which may be especially useful in patients with variceal hemorrhage (wherein volume loading may increase the pressure within the varix, thereby promoting further bleeding). One *in vitro* study found that PCC was more effective at restoring thrombin generation, compared to fresh frozen plasma. ([28537975](https://pubmed.ncbi.nlm.nih.gov/28537975/))

**tranexamic acid (TXA)**

- Tranexamic acid may be used if there is concern or evidence supporting hyperfibrinolysis (see the above section on acute intravascular coagulation and fibrinolysis). (REF)
- Tranexamic acid was not found to be generally beneficial for gastrointestinal hemorrhage in the HALT-IT trial. However, an ongoing study ([EXHAROSE trial](https://pubmed.ncbi.nlm.nih.gov/30099397/)) is evaluating whether tranexamic acid could be useful in the context of cirrhosis. For now, tranexamic acid should be restricted to patients in whom excessive hyperfibrinolysis is suspected.

**IV vitamin K**

- This should be given if there are any concerns for possible vitamin K deficiency (e.g., malnutrition, cholestasis, or prior warfarin use).
- The standard dosing is 10 mg IV as a slow infusion over 30-60 minutes.
  - 🔄 There is only one correct dose and route of vitamin K for a patient in the ICU with active hemorrhage: 10 mg, intravenously.

**massive transfusion protocol**

- In massive hemorrhage, a massive transfusion protocol (MTP) may be activated. This will result in rapid delivery of blood products in a 1:1:1 ratio of RBCs:FFP:platelets (with occasional supplementation of cryoprecipitate and calcium).
- The massive transfusion protocol is generally titrated against hemodynamic variables, and continued until the patient is no longer in severe shock.
- Following completion of the massive transfusion protocol, coagulation factors should be checked and managed as described above.

**coagulation management prior to a planned procedure**

**low-risk procedures**

- These may include the following:
  - Thoracentesis
  - Paracentesis
  - Routine upper endoscopy for variceal ligation
  - Central venous catheter insertion under ultrasound guidance
- The American Gastroenterology Association recommends against routinely correcting thrombocytopenia and coagulopathy before these procedures. However, this doesn't apply to pharmacologically anticoagulated patients and renal failure patients, who may be at increased risk of bleeding.
  - There is a large body of evidence that paracentesis and thoracentesis are generally safe in patients, even those with a combined elevation of INR and thrombocytopenia. Therefore, the risks of transfusion greatly outweigh the potential benefit ([30986390](https://pubmed.ncbi.nlm.nih.gov/30986390/)).
  - The guidelines don't actually discuss central venous catheter insertion, but central line insertion seems to be a lower-risk procedure compared to thoracentesis.
- The best approach to limiting bleeding:
  - Use the smallest bore needle possible (e.g., a 24-gauge lumbar puncture needle is adequate for diagnostic paracentesis).
Use ultrasound guidance with visualization of nearby arteries (e.g., visualization of intercostal arteries prior to thoracentesis, or visualization of the inferior epigastric artery prior to paracentesis).

The procedure should be performed by an experienced operator.

**higher-risk procedures (e.g., surgical procedures, lumbar puncture)**

- For more extensive procedures, the approach is similar to management of an active hemorrhage (see the section above)(REF).
- Blood products should be provided immediately before the procedure, as their effect will dissipate over time.

**DVT prophylaxis in cirrhosis**

Overall, the current consensus is that in patients with cirrhosis, the hemostasis is shifted towards a procoagulant state. ~[Zermatten MG et al. 2020](https://pubmed.ncbi.nlm.nih.gov/32090357/)

**key point: cirrhosis usually increases the risk of DVT**

- A common misconception is that since patients with cirrhosis have an elevated INR, they are “auto-anticoagulated” and don’t require DVT prophylaxis. This is not true!
- Cirrhosis may actually increase the risk of DVT with an odds ratio of 1.7. ([27761574](https://pubmed.ncbi.nlm.nih.gov/27761574/)) This could relate to numerous factors, such as deficiencies of endogenous anticoagulant proteins (e.g., protein C and protein S) and inflammatory activation of endothelial cells.
- Of course, not every patient with cirrhosis will be at increased risk of DVT – there is a tremendous degree of heterogeneity among these patients. But overall, this patient group is at high risk of DVT/PE and requires DVT prophylaxis.

**approach to DVT prophylaxis in cirrhosis**

- Critically ill patients with cirrhosis should generally receive chemical DVT prophylaxis, similar to other critically ill patients. However, DVT prophylaxis may be contraindicated in the following situations:
  - (1) Active bleeding
  - (2) Severe thrombocytopenia (e.g., perhaps platelets <30,000/μL)
    - One RCT demonstrated the safety of prophylactic enoxaparin (40 mg/day) among patients with cirrhosis who were treated for a year. Patients were excluded from the study only if their platelet count was <10,000/μL. With 70 patients the study is somewhat underpowered to evaluate rare safety endpoints, but it does support the safety of prophylactic-dose enoxaparin among patients with cirrhosis and thrombocytopenia ([22819864](https://pubmed.ncbi.nlm.nih.gov/22819864/)).
  - (3) Uncontrolled hyperfibrinolysis (e.g., fibrinogen <80 mg/dL)
  - (4) TEG showing a pathologically prolonged R-time
    - Elevated INR doesn't reveal anything about coagulation and generally shouldn't be a contraindication to anticoagulation.
    - A dramatically prolonged clotting time on *thromboelastography* suggests true enzymatic hypocoagulation — which would be a rational contraindication to DVT prophylaxis. However, this is a rare finding (and if detected might suggest another superimposed process). Thus, TEG isn't routinely required in all patients with cirrhosis prior to initiation of DVT prophylaxis. However, if there is concern about a dramatically elevated INR, then TEG is a rational approach to provide reassurance that enzymatic coagulation is adequate.

*There isn't any RCT-level evidence regarding the use of DVT prophylaxis in cirrhosis. When in doubt, clinical judgement is required to tailor therapy to the individual patient.*

Giving FFP with the goal of improving the INR is misguided in these patients. Most patients with an elevated INR do not have a problem with enzymatic coagulation.

Holding DVT prophylaxis in patients with prolonged INR, due to the misperception that patients are "auto-anticoagulated."

Failure to recognize hyperfibrinolysis ("accelerated intravascular coagulation and fibrinolysis") as a cause of persistent and refractory bleeding in occasional patients with advanced cirrhosis.

Excess attention to the INR, while ignoring the fibrinogen.

**Going further:**


