Coagulopathy in Chronic Liver disease

“Rebalanced Hemostasis”

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The Clotting Process

- Initiation and formation of the platelet plug
- Propagation of the clotting process by the coagulation cascade
- Termination of clotting by antithrombotic control mechanisms
- Removal of the clot by fibrinolysis
Coagulation with Thrombin Generation

1. Endothelial damage
2. Exposure to tissue factor
3. Initiation of extrinsic pathway
4. Initiate thrombin generation
5. Activate fibrinogen, intrinsic pathway
6. FXIII
7. Amplify thrombin generation

Diagram: Flowchart showing the stages of coagulation with thrombin generation.
Coagulation with Thrombin Generation and Inhibition
Platelet Abnormalities

• Decreased amount caused by:
  ▪ Splenic sequestration
  ▪ Decreased thrombopoietin
  ▪ Bone marrow suppression
  ▪ Autoantibody destruction (Hep C, autoimmune processes)

• Abnormal function
  ▪ Uremia, HRS
Hyperfibrinolysis in Liver Disease

• Patients with cirrhosis may have laboratory features of accelerated fibrinolysis, however, this is debated.

• Mild systemic fibrinolysis found in vitro in 35-40% of cirrhotic patient, it parallels degree of liver dysfunction
  - However clinically evident fibrinolysis seen only in 5-10%

• In ALI/ALF patients’ fibrinolytic capacity was found to be profoundly impaired compared to healthy controls, which was associated with decreased levels of the plasminogen and increased levels of plasminogen activator inhibitor type 1.

¹Thrombin-Activatable Fibrinolysis Inhibitor Deficiency in Cirrhosis Is Not Associated With Increased Plasma Fibrinolysis Lisman et al, Gastroenterology 2001
²Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure, Lisman et al, Journal of Thrombosis and Haemostasis 2012 10; 1312-9
Other Factors Determining the Risk of Bleeding

- Excessive NO, PG₁₂ production by endothelium
- Collateral veins in peritoneum
Rebalanced Coagulation in Chronic Liver Disease

- Chronic liver disease is characterized by decreased levels of most procoagulant factors with the exception of factor VIII and von Willebrand factor, which are elevated.
- Anticoagulant/fibrinolysis factors including antithrombin, protein C, ADAMTS13, plasminogen are also low.
- This resets the hemostatic balance despite an increase in the prothrombin time/INR.
INR/PT and PTT

- INR was devised and validated to standardize across laboratories the prothrombin times in patients receiving anti-coagulation therapy with vitamin K antagonists such as warfarin.
- INR reflects factors I, II, V, VII, X.
  - Vitamin K factors II, IX, VII, X, protein C, S.
- Has been validated as a prognostic marker for liver disease mortality, but not for bleeding risk.
INR/Prothrombin Time not Predictive of Bleeding Risk

• Basic laboratory tests PT/PTT correlate poorly with bleeding from various invasive procedures or gastrointestinal hemorrhage

• Fresh frozen plasma administration does not prevent or minimize procedural bleeding

• Elevated PT/INR in patients with liver cirrhosis does not mean “auto-anticoagulation”
54 year old male presents with increasing abdominal distention for the last two months. Denies fever, chills, abdominal pain, hematemesis or spontaneous bleeding episodes.

Past medical history is significant for alcohol abuse. Vital signs: BP 119/71, HR 83, RR 18, saturation 95% RA. Physical examination reveals non-tender, distended abdomen, with shifting dullness. Laboratory work up result: Hb 12.3, WBC 5.1, Plt 47,000, creatinine 1.0, INR 2.3.

Abdominal US confirms large volume ascites and shows cirrhotic appearing liver.

What is the next best step in management?

A. Start the patient on furosemide and spironolactone
B. Transfuse 2 units of FFPs, then perform paracentesis
C. Perform diagnostic and therapeutic paracentesis
D. Transfuse one unit of platelets, then perform paracentesis
Plasma Thrombin Generation Non-inferior When Compared to Healthy Controls

- Tripode et al, Gatt et al showed that plasma from patients with cirrhosis generates as much thrombin (the final enzyme of coagulation) as plasma from healthy subjects, provided that thrombin is measured by methods that reflect the action of both procoagulants and anticoagulants
Bleeding After Liver Biopsy

Bleeding After Liver Biopsy Does not Correlate with Indices of Peripheral Coagulation. Ewe K. May 1981
Large Volume Paracentesis in Coagulopathy

• 1,100 outpatient LVPs on 628 patients at Mayo Clinic by PAs
• 513 of the patients had cirrhosis of the liver
• INR ranged between 0.9 and 8.7
• Platelet count ranged between as low as 19 and 341, majority <50
• No blood products other than albumin were used
• No complications requiring hospitalization
Central Venous Catheterization in Patients With Coagulopathy

• Retrospective review of 40 liver transplant patients, total of 259 central venous catheterizations, 202 had coagulopathy
• Internal jugular and subclavian veins accessed, 7F-8.5F lines used
• Abnormal PT values ranged from 10% - 39% of control (normal range 65% to 130%)
• Average APTT 92 sec (normal range 21-31 seconds)
• Average abnormal PLT 47,000 (8,000-79,000)
• No correction of coagulopathy was performed
• No serious bleeding complications occurred
Central Venous Cannulation in Patients with Liver Disease

- 658 cannulations (352 subclavian, 306 internal jugular)
- Median INR 2.4 (1-16) in subclavian group, 2.7 (1-17) in IJ group
- FFP and given in 5 cases and platelets in 12 cases, INR and platelet measurements were recorded after transfusion
- Median platelet count 81 (9-108) and 83 (10-425) respectively
- Only one patient developed hemothorax after accidental subclavian artery puncture (INR 1.5, PLT 68)
- No other major vascular complications
Post-procedural Bleeding was Unrelated to Platelet or INR Counts in Patient with Liver Cirrhosis

- Prospective case series of 852 procedures carried out in 363 patients with liver cirrhosis
- 10 post procedure bleeds occurred in the whole case series
- PLT ranged from 3,000 to >100,000, highest INR 4.2
- Bleeding was unrelated to PLT count and INR values
- 10 patients with most profound alterations in PLT and INR had no post-procedural bleeding
- The only variable associated with bleeding was the number of invasive procedures

Bleeding After Invasive Procedures is Rare and Unpredicted by Platelet Counts in Cirrhotic Patients with Thrombocytopenia Napolitano et al, European Journal of Internal Medicine, December 2016
What Do the Guidelines Say?

- Because bleeding is sufficiently uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended by AASLD.

- Uptodate recommends against transfusion based on INR, rather use the value as prognostic marker. Also recommends PLT >50-55 for active, severe or central nervous system bleeding.

- Platelet transfusion should be considered when levels are less than 50,000-60,000/mL for transcutaneous or transvenous liver biopsy. The use of prophylactic or rescue strategies such as plasma, fibrinolysis inhibitors, or recombinant factors should be considered in specific situations, although their effectiveness remains to be established - AASLD.

- More and more centers report transfusion-free liver transplantation in a substantial proportion of patients.*

*Transfusion Rate for 500 Consecutive Liver Transplantations: Experience of One Liver Transplantation Center, Massicotte et al, Transplantation June 2012
Question 2:

61 year old male with past medical history of hepatitis C cirrhosis, HTN and HLD presented to the ER with right femoral fracture sustained in MVA. BMI is 25. Pre operative labs reveal Hb of 12, platelets 103, creatinine 0.9 and INR 1.9. The patient undergoes uncomplicated surgical repair. Post operative Hb level shows initial drop, however remains stable after 48 hours.

The DVT prophylaxis of choice would be:

A. Knee high sequential compression device
B. Subcutaneous heparin 5000 Units twice daily
C. Subcutaneous enoxaparin 40 mg daily
D. Graduated compression stockings
Increased Thrombotic Risk

- Decreased protein C and S
- Decreased anti-thrombin, thrombomodulin levels
- Elevated levels of vWF and FVIII
- Decreased degradation of activated coagulation factors
Increased Risk of Thromboembolism Seen in Patients with Liver Disease as Compared to Controls

- 99,444 patients with venous thromboembolism, 496,872 population controls
- Increased relative risk of venous thromboembolism, varying from 1.74 (95% CI, 1.54–1.95) for liver cirrhosis to 1.87 (95% CI, 1.73–2.03) for non-cirrhotic liver disease
- Higher risk for deep venous thrombosis compared with pulmonary embolism
- In the analysis, restricted to 67,519 patients with unprovoked venous thromboembolism and 308,614 population controls, slightly higher relative risks: 2.06 (95% CI, 1.79–2.38) for liver cirrhosis and 2.10 (95% CI, 1.91–2.31) for non-cirrhotic liver disease
Cirrhosis is Associated with an Increased Risk of Deep Venous Thrombosis and Pulmonary Embolism

- Systematic review and meta-analysis of 11 articles

- Enrolling a total of 695,012 cirrhotic patients and 1,494,660 non-cirrhotic controls

- Cirrhosis was associated with increased risk of DVT (OR: 2.038; 95%CI: 1.817 -2.285; p<0.0001) and PE (OR: 1.655; 95%CI: 1.042 -2.630; p=0.033)

- Male gender was regarded as a high-risk subset for VTE in cirrhosis
Thrombotic Complications

• Portal vein thrombosis
  Seen in 10-50% of cirrhotic patients
  DVT/PE can occur in 5% of hospitalized patients

• PVT is a poor prognostic sign in patients awaiting liver transplant, particularly complete PVT with extension to SMV
Anticoagulants Improved Outcome in Portal Vein Thrombosis

- Systematic review and meta-analysis of 8 studies (353 patients) in patients with cirrhosis and PVT
- LMWH/warfarin therapy as compared to no anticoagulation group yielded thrombus recanalization, lowered thrombosis progression as well as risk for bleeding
- Significantly higher proportion of patients treated with anticoagulants underwent PVT recanalization or complete resolution than patients who did not receive anticoagulants  $p < .0001$
- Six studies (257 patients) reported rates of any bleeding; no difference in the proportions of patients with major or minor bleeding between groups that did vs did not receive anticoagulants (11% for both groups)
- Four studies (comprising 158 patients) reported rates of spontaneous variceal bleeding, which occurred in a significantly lower proportion of patients who received anticoagulants vs those who did not; 2% vs 12% in anticoagulant- treated patients vs untreated patients, respectively (OR, 0.232; 95% CI, 0.06–0.94; $p = 0.04$)

Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis L. Loffredo et al. Gastroenterology August 2017
Rebalanced Hemostasis

Hemostatic changes promoting bleeding

- Thrombocytopenia, platelet dysfunction
- Enhanced production of nitric oxide and prostacyclin
- Low levels of coagulation factors II, V, VII, IX, X and XI
- Vitamin K deficiency
  - Dietary, absorption, lack of bile salts
- Dysfibrinogenemia
- Low level of alfa2-antiplasmin, factor XIII, TAFI
- Elevated tPA levels

Hemostatic changes promoting thrombosis

- Elevated levels of vWF
- Elevated FVIII
- Decreased levels of ADAMTS-13
- Decreased levels of protein C, S, antithrombin, alfa2-microglobulin and heparin cofactor II
- Low levels of plasminogen
- Decreased degradation of activated coagulation factors
Contributing Factors, Complications:

• Recognize superimposed conditions: infection, sepsis, uremia, hyperfibrinolysis

• Identify vitamin K deficiency in patients with poor nutritional status

• The patients with elevated standard coagulation test may still be at risk of thrombosis, despite apparent coagulopathy

• Elevated CVP
Thromboelastography (TEG)/Thromboelastometry (ROTEM)

• More comprehensive assessment of clotting derangements

• Measures
  ▪ Aggregation
  ▪ Clot strengthening
  ▪ Fibrin cross linking
  ▪ Fibrinolysis

• Does not necessarily correlate with standard coagulation tests
Interpretation of TEG

- **Normal**
  - R, K, MA, Angle = Normal

- **Anticoagulants/hemophilia**
  - Factor Deficiency
  - R, K = Prolonged;
  - MA, Angle = Decreased

- **Platelet Blockers**
  - Thrombocytopenia/
  - Thrombocytopenia
  - R = Normal; K = Prolonged;
  - MA = Decreased

- **Fibrinolysis (UK, SK, or t-PA)**
  - Presence of t-PA
  - R = Normal;
  - MA = Continuous decrease
  - Lyc 7.5%; WBC 100 < 97.5%;
  - Lyso 15.0%; WBC > 85%

- **Hypercoagulation**
  - R, K = Decreased;
  - MA, Angle = Increased

- **D.I.C.**
  - Stage 1
  - Hypercoagulable state with secondary fibrinolysis
  - Stage 2
  - Hypocoagulable state

- **Brandy Tumbler**
  - Do Nothing

- **Red Wine Glass**
  - Give FFP

- **Test Tube**
  - Give Platelets

- **Champagne Flute**
  - Give Cryp

- **Upside Down Martini Glass**
  - Give TXA

- **Thromboelastography in Trauma**
Adverse Effects of FFP Transfusion

• Allergic
  ▪ Usually mild, high level IgE – storage-induced changes in plasma proteins
• Anaphylactic
  ▪ Antibodies to IgA, may need IgA-free FFP in the future
• Febrile, non-hemolytic
• Transfusion Related Acute Lung Injury (TRALI)
  ▪ FFP transfusion associated with TRALI in ESLD*
• Transfusion Associated Circulatory Overload (TACO)
• Increase in portal pressure by 1mmHg with each unit of FFP

*Transfusion-related Acute Lung Injury in ICU Patients Admitted with Gastrointestinal Bleeding, Benson et al Intensive Care Medicine, July 2010
Effect of Renal Failure

• Abnormalities seen of platelet structure
  ▪ Lower than normal ADP and serotonin in granules: decreased thromboxane A2 generation
  ▪ Dysfunction of glycoprotein GIIb-IIIa: membrane glycoprotein important in aggregation and adhesion

• Platelet NO synthesis increased: inhibits platelet aggregation and adhesion
Factor Levels

• Factor VIII can help distinguish DIC from liver failure: decreased in DIC and normal or increased in cirrhosis

• Factor V and VII: greater reduction in factor VII than FV favors vitamin K deficiency
  - Factor VII half life ~ 6 hours
  - Factor V half life ~36 hours

• Fibrinogen level < 120mg/dL associated with diminished clot formation – treat with fibrinogen rich cryoprecipitate
Potential Interventions

- Platelet transfusion
  - For moderate risk procedures >50,000
  - For high risk procedures > 100,000
- Cryoprecipitate
  - Less volume than FFP
  - Useful in patients with fibrinogen <120mg/dL
- FFP, lack of predictable effect:
  - Conventional doses correct cirrhotics in only 10-20%
  - Risk of volume overload
  - Risk of TRALI
- Prophylactic antibiotics in UGI bleed
- Maintain low CVP, normal Ca, pH levels

- Aminocaproic acid or tranexamic acid in hyperfibrinolysis
- Desmopressin in uremia
- Prothrombin complex concentrate
- Fibrinogen concentrate

<table>
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<tr>
<th>Comparison of Fresh Frozen Plasma and Cryoprecipitate</th>
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<tbody>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td>250 to 300 mL</td>
</tr>
<tr>
<td><strong>Time to prepare</strong></td>
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<tr>
<td>30 minutes</td>
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<tr>
<td><strong>Fibrinogen</strong></td>
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<tr>
<td>700 to 800 mg</td>
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<tr>
<td><strong>Other coagulation factors</strong></td>
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<tr>
<td>All, including factors II, VII, VIII, IX, X, XI, and vWF</td>
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In Summary:

• Do not correct INR/platelet counts in clinically stable patients

• If bleeding occurs (GI, airways) look for potential alternative causes
  ▪ Varices, portal hypertensive gastropathy/colopathy

• More sophisticated (viscoelastic) tests may provide a better answer

• Consider pharmacological DVT prophylaxis
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Thank you.