Coagulation and liver disease

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Objectives

• Basic concepts in hemostasis
• Changes in hemostasis with liver cirrhosis
• Review of coagulation tests and their applicability
• New products available
• Practical clinical recommendations
Clinical Problems

- Hepatitis C and B
- Alcoholic cirrhosis
- PBC, PSC, HCC
- NASH
- Acute liver failure

- Paracentesis
- Esophageal varices
- TIPS
- Dental extractions
- Liver transplant
- Elevated ICP

- Portal vein, Hepatic artery thrombosis
- DVT and PE

Hemostasis

- Complex apparatus
- Not entirely understood
- Interaction of multiple organs
- Regional and systemic variations

Hemostasis – classic view
Hemostasis – Cell Based Model

• Step 1 Primary Hemostasis
  – Initial plug of vascular breach
  – Activated platelet
  – Thrombin burst
  – Initial critical step

**Hemostasis**

**Pro-Coagulation**
- Liver Dependent
  - Coagulation Factors
  - Clearance activated tPa, α2-antiplasmin.
- Liver Independent
  - Tissue Factor
  - Factor VIII
  - Factor vW
  - Platelets number and function

**Anti-Coagulation**
- Liver Dependent
  - Protein C, S, AT III, clearance of activated Factors. (Modulators)
  - Plasminogen (Fibrinolysis)
- Liver Independent
  - tPa (Fibrinolysis)
  - Tissue factor path inhibitor (Modulator)

**Hemostasis – Balanced system**

**Changes with Liver Disease**

- Pro-Coagulation changes
- Anti-coagulation changes
Changes with Liver Disease

• Primary Hemostasis
  – Endothelium:
    • Poor flow
    • Chronic inflammation
    • Decrease in thrombomodulin


Changes with Liver Disease

• Primary Hemostasis
  – Platelet adhesion
    • Increase in platelet adhesion molecules (vWF)


Changes with Liver Disease

• Primary Hemostasis
  – Platelet activation and thrombin burst:
    • Normal production in plasma from ESLD patients, when assay includes thrombomodulin
    • Normalized in vitro when platelets 55-100k

Changes with Liver Disease

• Fibrin mesh:
  – Low anti-coagulantion factors
    • II, V, VII, IX, X, and XI
  – Low protein C, S, AT3,
  – Low clearance of activated factors
  – Low coagulation factors
  – Abnormal polymerization: Excess abnormal fibrinogen and low F-XIII

Changes with Liver Disease

• Fibrinolysis:
  – Decrease clearance activated tPa, α2-antiplasmin.
  – Low levels of plasminogen

Changes with Liver Disease

• The rebalanced state
  – Liver disease is at the tipping point due to less reserve
  – Although compensatory mechanisms are active, the capacity to adjust to insults to the system is diminished, and small perturbation can overcome compensatory mechanisms

Changes with Liver Disease – Re-balanced System

Liver Transplant Case

• 59yo M admitted to the hospital for HE, N/V, diarrhea, hyperbilli and anemia
• s/p OLT for cirrhosis secondary to HCV type 1
• Post OLT has been c/b recurrent HCV in the form of fibrosising cholestatic HCV but no rejection. On triple therapy, could not be completed due to side effects.
• MELD Score: 38
• PMH: DM2, He also had an episode of SVT treated with adenosine.

Liver Transplant Case – Pre-Anhepatic

Platelet hypocoagulability
Liver Transplant Case – Anhepatic phase

- Consumption Coagulopathy
  - Constant activation of intrinsic pathway
  - Deficiency of AT III
- Progressively increased fibrinolysis
  - Rapid rise in tPa levels
Liver Transplant Case – Anhepatic phase
Secondary fibrinolysis secondary to hypercoagulable state, normal reaction time, platelet hypocoagulability

Liver Transplant Case – Reperfusion
• Pro-coagulation
  – Post-reperfusion syndrome: sudden and temporary activation of the coagulation system
  – Low flow state
• Anti-coagulation
  – Consumed AT III
• Fibrinolysis
  – Most pronounced immediately before and after reperfusion, recovery is fast

Liver Transplant Case – Reperfusion
Secondary fibrinolysis secondary to hypercoagulable state, normal reaction time, platelet hypocoagulability
Liver Transplant Case – Cardiac Arrest

Liver Transplant Case – PostOperative Course

- **Brain Function:** AOx2, delirious and violent, requires help for ADL, weak and deconditioned, dysphagia.
- **New Liver Function:** No new issues. Tolerating immunosuppression.
- **Kidney Function:** Estimated GFR: >60, however AKI requiring HD on 09/25.
- **Heart Function:** NSR, No new findings on echo.
Bleeding and Clotting Risk?

- Clinical evaluation
- Laboratory tests
- Nature of the procedure
- Institutional and practice guidelines

Laboratory Tests

- Things you usually check
  - Low platelet count
  - High INR (low 2,5,7,9,10)
  - Low fibrinogen
  - Normal PTT

- Things you usually don’t check
  - High vWF and VIIIa
  - Low levels of protein C and antithrombin III
  - Elevated levels of plasminogen

Laboratory Tests

- Not widely used:
  - TEG
  - Sonorheometry
  - PFA-100
  - Anti-Xa assay
  - Bedside whole-blood clotting times

- Experimental
  - Endogenous thrombin potential
  - Euglobin lysis time
  - Procoagulant microparticles assays
Laboratory Tests - INR

- INR is a poor predictor of bleeding
- 121 ESLD patients
- Thrombocytopenia
  - <150k in 84%
  - <75k in 51%
- 50 of these underwent procedures
  - 10 (20%) bled
  - All had platelets <75k
- INR >1.5 was not associated w/ bleeding
- 2U of FFP pre-procedure is of little benefit for INR 1.5 – 1.7


Laboratory Tests - INR

- Numerous studies affirming lack of utility
  - Percutaneous, laparoscopic and open liver biopsy, renal biopsy
  - Paracentesis
  - Colonoscopy and polypectomy
  - PEG
  - Dental extractions
  - Bronchoscopy
  - Arteriography and angioplasty

Laboratory Tests - INR

- Problems with INR
  - Designed for warfarin therapy
  - Variability across different labs
  - Better indicator of progression of disease (protein synthesis), not risk of bleeding

Laboratory Tests – Fibrinogen

- Low levels of fibrinogen
  - Common in stable non-bleeding patients
  - Low grade DIC:
    - Not a common feature of stable liver cirrhosis
    - Laboratory findings suggestive of DIC are predominantly a reflection of decreased hepatic clearance of activation products.
  - Acute phase reactant


Laboratory Tests - TEG

- Advantages
  - Time tested for quick diagnosis and guidance of coagulation issues
  - Can detect hypercoagulability, however it can miss some patients
  - Can detect primary and secondary fibrinolysis
  - Can detect platelet function inhibition

- Disadvantages
  - Rotational shear not natural
  - Whole blood test, fast turnaround of samples
  - Might miss some hyper-coagulable patients
  - Not validated outside of the OR or acute settings
### Laboratory Tests – Whole blood clotting times

**Advantages**
- Low cost, supplies universally available, red top tube
- Tip gently... no running liquid...
  - Good clot at 20min... mild or no coagulopathy
  - Clot at <10 min... hyper-coagulable test
    - In combination with abnormal hypo-coagulable lab values. e.g. INR>3

**Disadvantages**
- Time consuming, unable to differentiate between platelet and factor deficiency
- Difficult to diagnose fibrinolysis

### Laboratory Tests – PFA-100

- Not calibrated for thrombocytopenia
- Not studied extensively in liver disease

### Laboratory Tests - Experimental

**Sonorheometry**
- Advantages
  - Same as TEG
  - More accurate detection of patients at risk for clotting events and effectiveness of DVT prophylaxis
  - More user friendly

- Disadvantages
  - Experimental
Laboratory Tests - Experimental

- Endogenous thrombin potential
- Euglobin lysis time
- Microparticles
  - Platelet derived
  - Tend to vary with severity of disease, More prevalent in Child C
  - Tend to be higher by flow cytometry in hypercoagulable patients


Correction of Coagulation

- FFP
- Cryoprecipitate
- Platelet
- Aminocaproic acid
- LMWH
- Warfarin
- Desmopressin
- PCC
- FVIIa
- Eltrombopag

Correction of Coagulation - FFP

- Prepared from a single unit of blood
- Contains all of the coagulation proteins
- Through storage and thawing processes, 40% degradation of coagulation factors
- INR = 1.3
Correction of Coagulation - FFP

- Limitations of FFP to correct INR
  - Half life of FVII in plasma is 5h
  - Bottleneck of the system
  - Correction of INR from 3.0 to 1.5 would require 2000ml (10u FFP).
  - Degradation of FVII of the first unit would likely be present by the time the 5-6th unit is being administered.
  - “only 50% of patients with an INR of 1.7 showed a significant change in INR with FFP transfusion”.


Correction of Coagulation - Cryo

- Cryoprecipitate good option for the complications with RBC transfusion:
  - Low fibrinogen, vWF, FXIII, Protein C
- Byproduct from thawing FFP
- Contains concentrated factor VIII, fibrinogen, XIII, vWF and others

Correction of Coagulation - LMWH

- Higher potency in cirrhotic
  - Increases with severity despite having low levels of Antithrombin III
  - More severe, more frail balance, same dose increased effect
- Anti Xa not useful.
  - Experimental use of Endogenous thrombin potential

Correction of Coagulation

- Aminocaproic acid:
  - Prophylactic low dose 5 min after reperfusion
- rFVIIa:
  - Fulminant failure + need for bolt
  - Cannot be recommended for general use
- Warfarin
  - Narrow therapeutic regimen
  - High rate of complications

Correction of Coagulation

- PCC: Factors II, VII, IX and X, as well as protein C and S
  - Currently being studied as a supplement for liver transplants, trauma, cardiac and brain surgery
  - Quick reversal of warfarin, and newer oral anticoagulants
- FEIBA: Factor eight inhibitor bypass activity: proenzymes of the prothrombin complex factors, prothrombin, FVII, FIX and FX,

Correction of Coagulation

- Eltrombopag reduced the need for platelet transfusions in patients with chronic liver disease who were undergoing elective invasive procedures, but it was associated with an increased incidence of portal-vein thrombosis, as compared with placebo

Clinical Recommendations

• 60yo F pre-transplant evaluation
• ESLD, CKD/dialysis
• Full mouth extraction
• **MELD 20**, s/p TIPS and s/p Esophageal varices banding no bleeding
• Htc 27, INR 2.1, and platelets 43k
• Delayed to get platelets and FFP through a mediport
• s/p 4x FFP and 4x Plt.
• Now pushed till 3am...
• EBL 100cc... no complications, normal TEG.

Clinical Recommendations – Prognosis

• SBP mortality / episode 40%
• GI Bleed: 30% mortality with each episode
• Hepatorenal syndrome, type I: median survival 2 weeks
• Versus survival with LT: 80% at 3yrs

Clinical Recommendations –
Prognosis

• With development of ascites: 50% two year survival
• Ascites refractory of diuretics: 25% one year survival


Clinical Recommendations - Decision

• MELD <11: proceed with elective surgery
• MELD 12-19 or Child B: complete transplant work-up, “these patients should preferably have surgery at an institution with liver transplant center”
• MELD >20 or Child C: postpone elective surgery until after transplant


Clinical Recommendations

• Acute liver failure
  • Despite profound elevation in INR, minimal global effects on hemostasis
  • Prophylactic correction not recommended except if active bleeding
  • High risk procedures
    • Single rFVIIa dose (40μg/Kg)
Clinical Recommendations – Bleeding Risk

• There are no good measures of bleeding risk before invasive procedures
• Decision to proceed with elective or semi-elective procedures
  – Not solely on INR and platelet count
  – Severity of comorbidities
  – Urgency of procedures
  – Access to mechanical hemostatic maneuvers
  – Ability to detect bleeding early

Clinical Recommendations – Bleeding Risk

• Pre-procedure Prophylaxis
  – For truly elective procedures, delay during acute events that might upset the rebalanced state
    • Acute infection, severe acute alcoholic hepatitis, uremia.
  – For dental extractions, FFP vs nasal desmopressin
    • As effective and more convenient
  – Platelet count >50-60k probably more appropriate for prophylaxis than INR alone
    • No added benefit when platelets >100k

Clinical Recommendations – Bleeding Risk

• Pre-procedure Prophylaxis
  – Protocol transfusions to correct INR are not helpful and are possibly harmful
  – rVIIa has not been shown to be beneficial in preventing bleeding complications
    • Acute liver failure patient requiring ICP monitoring (40mcg/kg)
Clinical Recommendations – Bleeding Risk

• Pre-procedure Prophylaxis
  – Society of interventional Radiology:
    • Correction of INR>2.0 with FFP for moderate to high-risk procedures

• Active Bleeding
  – Transfuse to Hb>7
    • Avoid overtransfusion injuries
  – Transfuse to Platelets >50-100
    • Will use 2-3 units in most decompensated cirrhotics
  – Fibrinogen >100-150
  – Correct INR if bleeding persists
    • About 10cc/kg of FFP
    • Large volume FFP might make pHTN worst

• Active Bleeding
  – With microvascular bleeding assess for hyperfibrinolysis (TEG)
  – rVIIa in special rare cases with thrombosis caveat
Clinical Recommendations – Bleeding Risk

- Esophageal Variceal Bleeding
  - Most common bleeding event in ESLD
  - Risk factors are hemodynamic and mechanic
    - pHTN gradient, varix size, appearance and severity of ESLD
    - Not necessarily coagulopathy
  - No specific recommendations for correction of anticoagulation before banding
    - Non-selective β-blocker for primary bleeding prophylaxis

Clinical Recommendations – Clotting Risk

- There are no good measures of clotting risk
- Decreased protein C
  - Levels similar to those with congenital deficiency
  - Worsens with severity of cirrhosis
- Increased FVIII
  - FVIII: Protein C ratio: became more unfavorable toward coagulation with increasing child scores.
- Resistance to Thrombomodulin


Clinical Recommendations – Clotting Risk

- Deep Venous Thrombosis (DVT)
  - Platelet count, INR and MELD: poor predictors of DVT and PE
  - Low albumin level <2.8g/dL, rough indicator
  - Consider medical prophylaxis in inpatients
    - Do not assume hospitalized patient is auto-anticoagulated
    - Treatment should follow the same protocol and similar doses as PE

Clinical Recommendations – Clotting Risk

• Portal Vein Thrombosis (PVT)
  – PVT is a frequent (10–20%) complication of liver cirrhosis
    • Highest risk, is malignancy, 6 month screening in all HCC patients
    • No evidence to support chronic anticoagulant therapy in asymptomatic patients
      – Bleeding risk is substantial, benefit of removing an asymptomatic PVT in cirrhosis is highly uncertain.


Clinical Recommendations – Clotting Risk

• Portal Vein Thrombosis (PVT)
  – May worsen its clinical course by favoring gastrointestinal bleeding and mesenteric infarction.
    • Treatment (LWMH) only in life-threatening thrombosis of the extra-hepatic portal district (acute or subacute, superior mesenteric and splenic veins)
    • Anticoagulation should be considered in patients with occlusive PVT awaiting transplantation
    • Esophageal varices must be resolved before therapy

Clinical Recommendations – Clotting Risk

• Post-transplant hepatic artery thrombosis
  – Devastating injury: Loss of graft
  – Risk factors:
    • Graft/surgery related: lengthy benchwork present and reperfusion time.
    • Recipient related: male, increase cold ischemia time, pre-existing DVT, albumin <2.5
Clinical Recommendations – IntraOperative Management

• Restrictive fluid regimen decreases portal venous pressure
• Phenylephrine helps to maintain arterial BP without increasing portal venous pressure
• Suggest surgical alternatives
   – Laparoscopic versus open


Clinical Recommendations - IntraOperative Management

• Aggressive infection prevention measures
  – Sterile techniques
  – Remove / avoid central access
  – Discontinue foley ASAP
• Maintain renal function / avoid nephrotoxic agents

Thank You
References


