Coagulation disorders in liver disease

• Prophylaxis?

• Treatment?

• Dr Ehsani

• Gastroenterologist
Intervene or not?

• Do not intervene
  - Asymptomatic elevations in the PT/INR, aPTT
  - Platelet count
  - That are thought to be due to the underlying liver disease

• An exception
  - Vitamin K deficiency
    - Poor nutrition and cirrhosis
    - Cholestatic disease
    - Diarrheal illness
    - Antibiotic use
Do not administer FFP

- To "correct" an abnormal PT/INR
- Possible risks and costs of this approach
  - Transfusion reactions
  - Volume overload
  - Increased portal pressures
- Lack of good quality evidence that it provides any clinically important benefit
Further investigation or intervene

• Large or unexpected changes
  - Newly prolonged PT or aPTT
  - New decline in platelet count

• Causes
  - Infection
  - New medication(s)
  - Portal vein thrombosis
  - Progression of the underlying liver disease
Severe thrombocytopenia / causes
Platelet count <50,000/microL

- Severe hypersplenism
- Medication reaction (IFN-based therapy)
- Complications (PVT, DIC, HIT)

- Close observation in the absence
- Of bleeding
- Of imminent procedure

- Not platelet administration
- Unless platelet count <10,000 to 15,000/microL
Liver disease versus DIC

• Clinical judgement
  □ Plays a major role

• Some laboratory features
  □ Factor VIII levels
  □ D-dimer levels (normal / mildly elevated in liver disease)

• Coexist  Liver disease and DIC
  □ Infection/sepsis / malignancy
Medications to avoid
Unless the benefits clearly outweigh the risks

- Increase bleeding and/or thrombotic risk
  - \textbf{NSAID} for routine treatment of pain / fever
  - Antiplatelet drugs
  - \textbf{Over-the-counter medications} (eg, ginkgo biloba)
Bleeding / General approach

- Depends on
  - Location
  - Severity
  - Degree of hemostatic impairment

- Variceal bleeding
- Nonvariceal bleeding
Bleeding ...answer the following questions

- Other comorbidities (eg, infection, uremia)
- Vitamin K deficient
- Status of fibrinogen
  - Level and function
  - Hyperfibrinolysis (especially with body cavity or puncture wound bleeding)?
- Platelet count
Bleeding approach....

- Comorbidities
  - **Infection**: vascular function, endogenous heparinoids, platelets
  - **Uremia**: impairs normal platelet function
Bleeding approach....

• Portal hypertension

Avoid raising portal pressures
Bleeding approach....

- Anatomic abnormality
  - Address any anatomic abnormalities that may be contributing

- DIC
  - Identify and treat the underlying cause

- Anticoagulation
  - Interrupt anticoagulation
  - Reverse the anticoagulant
  - Individualized according to the underlying indication for the anticoagulant and the severity and site of bleeding
Bleeding approach....

Anticoagulant

• Discontinuation/reversal
  □ More severe bleeding
  □ Less need for anticoagulation (e.g., active gastrointestinal bleeding, perioperative venous thromboembolism prophylaxis)

• Continuing the anticoagulant
  □ Greater need for thromboprophylaxis
  □ Less severe bleeding (e.g., mechanical heart valve, epistaxis)
Clot formation

Decide

• Which hemostatic products to administer?
  □ Mechanism identified
  □ Deficiency that is contributing to impaired clot formation

• Rather than a single laboratory measurement
Vitamin K

• 10 mg by slow intravenous infusion (ie, no faster than 1 mg/minute)

• Minor bleeding

☐10 mg orally / day for three days
Cryoprecipitate

• Active or poorly controlled bleeding
• One bag per 10 kg of body weight

While awaiting the results of laboratory testing for correction of presumptive hypofibrinogenemia or dysfibrinogenemia
Cryoprecipitate

- Maintain a fibrinogen level $\geq 100$ to $120$ mg/dL
- Persistent bleeding despite a fibrinogen level $\geq 100$ to $120$ mg/dL
Generally avoid

- Prothrombin complex concentrates (PCCs)
- Recombinant activated factor VII (rFVIIa)
  - Greater risk of promoting thrombosis
  - Costly
  - Not meaningfully affect outcomes
- May be used on a case-by-case basis
  - If bleeding continues despite other interventions
Generally avoid giving FFP

- Indications
  - Unexplained bleeding that persists after fibrinogen has been repleted with Cryoprecipitate
  - In patients requiring large numbers of red blood cell (RBC) transfusions
Platelets

- Maintain a platelet count
  - $>50,000$ to $55,000$/microL
  - $>100,000$/microL
- Active, severe bleeding
- Central nervous system bleeding

- Platelet function defects
  - If bleeding is severe and platelet function is thought to be impaired, platelet transfusion may be appropriate
RBC

• Maintain a hemoglobin level above 7 g/dL
• Higher target levels of hemoglobin
  □ In certain circumstances
  □ Coexisting vascular disease
Fibrinolysis

• High suspicion for hyperfibrinolysis
  □ Delayed bleeding
  □ Persistent oozing from mucocutaneous sites or puncture wounds

• Excess fibrinolysis
  □ Dental procedures
  □ Oral/mucosal bleeding
Fibrinolysis

- Suspected hyperfibrinolysis
- Clinical
- Laboratory features
- Antifibrinolytic agent
  - Tranexamic acid
  - Epsilon aminocaproic acid
- Intravenously or orally, or in soaked gauze (eg, during dental procedures)
Variceal bleeding

• Major cause
  □ Local vascular deformations
  □ Hemodynamic changes (eg, increased portal pressure)

• Bleeding diathesis
  □ Less common
Variceal bleeding

- Hemostatic mechanisms
  - Transient role
- Prevention and treatment
  - Reducing portal pressure
  - Ligating bleeding lesions
Rescue therapy

• Active bleeding despite these interventions
  ☐ Prohemostatic agents
• Potential benefits
• Risks
  ☐ Increased portal pressure with plasma transfusions
  ☐ Increased thrombotic risk with coagulation factor concentrates
Invasive procedure

General approach

• FFP to "correct" the PT/INR?
• General practice
  □ Optimize renal status
  □ Treat comorbidities (eg: infections)
  □ Rely on global measures of clot formation if available (or fibrinogen and platelet count if not)
  □ Avoid engorgement of the collateral bed as much as possible by limiting volume expansion
• Platelets
  □ Between 50,000 and 100,000
  □ Improved thrombin production and provide a rational target together with adequate thrombin substrate (fibrinogen)
Other interventions

• Mucosal engorgement of the capillary bed in the tributaries of the portal venous system
  - **Octreotide** 50 mcg as a single bolus, without an infusion
  - Just before interventions (biliary sphincterotomy and high-risk polypectomy)

• High-quality evidence
  - Lacking
Liver biopsy

- A review of 200 patients
- **No correlation** between the degree of bleeding and any measure of hemostasis tested (e.g., PT, platelet count, whole blood clotting time)
- **Using platelet transfusions**
  - To increase the platelet count to >50,000/microL,
  - Especially if there is known history of easy bruising or bleeding
- **Transfusing Cryoprecipitate**
  - To raise the fibrinogen to >120 mg/dL
- **Optimizing renal function**
- **Transvenous biopsy**: an alternative approach
Thoracentesis

- More dangerous than paracentesis: slightly
- **Approach:** similar to liver biopsy
  - Platelet transfusions to increase the platelet count to >50,000/microL
  - Cryoprecipitate to raise the fibrinogen level to >120 mg/dL
  - Optimizing renal function
  - Controlling infection
Dental extractions

- Addressing comorbidities
- Intranasal desmopressin (DDAVP)
- TEG or ROTEM: reassure operators in these moderate risk procedures

- A trial that randomly assigned 43 patients with cirrhosis awaiting liver transplantation who had an INR 2.0 to 3.0 and/or a platelet count ≤50,000/microL to receive intranasal DDAVP (300 mcg) or transfusions (FFP, 10 mL/kg and/or one unit of single donor platelets, based on INR and platelet count) prior to the dental procedure. Hemostasis was similar in the two groups, and adverse effects were less with DDAVP.
Palliative drain placement

- Better control refractory ascites
- Prophylactic therapy
  - May be warranted especially if a tunneled catheter is to be placed due to increased risk of trauma to the portal venous collateral bed of the abdominal wall
- Recommendation
  - Similar measures as outlined above for liver biopsy or dental extractions
Major surgery

- TEG and ROTEM
  - Guide optimal hemostatic measures
- In the absence of these tests
  - Optimizing the platelet count
  - Fibrinogen level
  - Renal function
  - Avoiding the use of INR values to guide therapy
  - Avoidance of volume expanding the portal collateral circulation
- TIPS: in selected patients / No controlled trials
Therapeutic Paracentesis

• Relatively low risk
  ○ Do not use preprocedure prophylaxis
• Exceptions
  ○ Patients who have bled before with paracentesis
  ○ Have known or suspected hyperfibrinolysis
  ○ Other overtly evident bleeding diathesis (mucosal bleeding or past bleeding with puncture wounds)
• Bleeding: venous from the collateral bed of the abdominal wall
  ○ Avoiding engorgement of the collateral bed (as with plasma transfusions)
Portal vein thrombosis

• 16 percent per year
  □ In stable cirrhosis without HCC
• Up to 40 percent in cirrhosis: overall
• Acute or chronic
• Focal left or right branch PVT
  □ More common
  □ Clinically silent
  □ Contribute to overall organ atrophy
Mechanism of PVT
Combination of factors

• Reduction in natural anticoagulants
• Decreased blood flow in the portal circulation
• Inflammatory changes that alter endothelial integrity
• Other prothrombotic comorbidities in some individuals

• Clinical significance of PVT
  □ Debated (epiphenomenon or a treatable condition)
• Need for therapy
  □ Obvious symptoms
PVT risk factors

• Liver disease
• Greater disease severity
• HCC
• Genetic susceptibility factors (eg, inherited thrombophilia)
• Higher incidence of factor V Leiden mutation (cirrhosis and PVT)

☑ In case controlled study
Testing for genetic thrombophilic factors

- Incompletely defined
- Test for the most prevalent (eg, factor V Leiden mutation and prothrombin mutation)
- PVT unrelated to cancer
- Candidates for anticoagulant therapy
- To help guide duration of therapy
PVT prophylaxis

- Optimizing hepatic function
- Reducing portal venous pressure
- Increasing portal flow
  - Diminishes stasis
- Role of prophylactic anticoagulation
  - Uncertain
  - Not routinely used
Separate indication for anticoagulation

• Cirrhosis is not a contraindication

☐ Assessment and treatment of high-risk varices if present

☐ A randomized trial to address the role of anticoagulation to prevent PVT was conducted using fixed-dose low molecular weight (LMW) heparin (enoxaparin 4000 international units subcutaneously once daily) versus no therapy for one year in 70 patients with advanced cirrhosis (Child-Pugh class B, mean model for end-stage liver disease [MELD] score 13). Portal vein patency was documented prior to entry
Separate indication for anticoagulation

• Greater reduction in the incidence of PVT by ultrasound and computed tomography (the primary endpoint) was seen with enoxaparin compared with controls at all time points: one year (0 versus 17 percent), two years (0 versus 28 percent), or study end (approximately three and a half years; 9 versus 28 percent).

• Secondary endpoints including hepatic decompensation (eg, development of ascites, encephalopathy, peritonitis)
  □ Less frequent with enoxaparin (12 versus 59 percent), and there was a
  □ Modest but significant improvement in survival (8 versus 13 deaths).

• Complications of enoxaparin
  □ Minimal, with no episodes of severe bleeding and one episode of thrombocytopenia that led to discontinuation of enoxaparin.
  □ Two enoxaparin-treated patients and one control patient had variceal bleeding.
Separate indication for anticoagulation

- Trial was small
- Focused on patients with moderate disease (mostly Child-Pugh B or early C)
- Methodological concerns including premature data analysis, atypical patient population, un-blinding
- The results cannot be regarded as clinically compelling

- Routine use of prophylactic anticoagulation for PVT

☐ Not recommended
Venous thromboembolism (VTE)

- Cirrhosis is not fully protective
- DVT incidence
  - 0.6 percent
- PE incidence
  - 0.28 percent
- Heterogeneity among various studies
VTE prophylaxis

• **Appropriate** for the majority of hospitalized medical and surgical patients with liver disease

• **Similar** to individuals hospitalized with other acute conditions

- In a study of 235 patients with chronic liver disease (mean model for end-stage liver disease [MELD] score, 16.2) who were hospitalized 355 times and received VTE prophylaxis as part of an institution-wide protocol.

  - Approximately three-fourths received unfractionated heparin, and the remainder received a LMW heparin

  - Nine episodes of gastrointestinal bleeding (2.5 percent), most of which were minor (<2 g/dL decline in hemoglobin), and

  - Two episodes of heparin-induced thrombocytopenia (HIT; 0.5 percent).

  - Five patients (1.4 percent) developed a VTE despite prophylaxis.
Exceptions to the use of VTE prophylaxis

- Severe thrombocytopenia (eg, platelet count <50,000/microL)
- Active bleeding
- High-risk varices (eg, red wale marks, stigmata of recent bleeding)
VTE therapy

- Concerns about risk of bleeding
- Difficulty monitoring the degree of anticoagulation
- Lack of evidence to support a specific anticoagulant, dose, or duration of therapy
- Balance the risks and benefits of anticoagulation
  - Presence or absence of varices
  - Screening endoscopy if this has not been performed already
  - Vena caval filter may be appropriate if the thrombosis is in a peripheral deep vein: controversial
- Removable filters, in acute setting
VTE therapy

- No significant varices
- Warfarin
- Direct acting oral anticoagulant (dabigatran, apixaban, rivaroxaban, edoxaban)

Less commonly

- Choice of anticoagulant and duration of therapy

Determined through collaboration of hepatologists and hematologists
VTE therapy
Monitoring

• Which anticoagulant
• Baseline testing
• NL range INR
  □ Warfarin can be used
  □ Target INR levels: 2.0 to 3.0
• INR out of the normal range
  □ Other anticoagulant
• Warfarin in patients with baseline INR prolongation (eg, patients with prosthetic heart valves or atrial fibrillation)
  □ low doses with a target INR of up to 3.5
VTE therapy

Monitoring

- LMW heparin
- Therapeutic doses
  - Measure anti-factor Xa activity
Decompensated cirrhosis

- Safety of therapeutic anticoagulation for DVT and PE
  - Not been determined
- Bleeding risks
  - Relatively low
- Higher doses of heparin products
  - Mild antithrombin deficiency (some patients)
Hemostatic profiles in Acute liver failure

- Not similar to chronic liver diseases
- Thrombin generation capacity
  - Intact
- Thromboelastography
  - Normal hemostasis
- Rate of bleeding with intracranial pressure monitoring
  - Similar in the group that received INR correction with significant amounts of FFP transfused as the group that did not receive (in one study)
Thanks for your attention