Anticoagulation in patients with cirrhosis: balancing the risks of bleeding and thrombosis

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Disclosures

I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation

Objectives

Pharmacist learning objectives

1. Describe the pathophysiology of coagulopathies in hepatic cirrhosis and acute liver failure.
2. Evaluate the safety and efficacy of using anticoagulants in patients with patients with cirrhosis.

Technician learning objectives

1. Describe the major complications of coagulopathies in patients with cirrhosis.
2. Recognize anticoagulants that may be used in patients with cirrhosis.

Patient case

A 32 year-old male with Child-Pugh class C liver disease and a Model for End-stage Liver Disease (MELD) score of 30 presents to the emergency department with sudden-onset abdominal pain. A contrast-enhanced abdominal computated tomographic scan is obtained that shows acute portal vein thrombosis. Laboratory results of interest reveal an INR of 2.2, serum creatinine 1.3 mg/dL, serum albumin 3.2 g/dL, platelet count 65 x10^9/L, and serum bilirubin 18 mg/dL. Which of the following might you recommend?

a) Enoxaparin 1 mg/kg SQ BID
b) Apixaban 10 mg BID for 7 days followed by 5 mg BID
c) Heparin IV bolus and infusion with transition to warfarin
d) No anticoagulation

Hemostasis and the liver

- Liver is responsible for majority of factors associated with hemostasis
  - Anticoagulants (Proteins C and S)
  - Procoagulants (Factors I through XII)
- Other non-hepatic factors
  - vWf, antiphospholipid antibodies, tissue factor pathway inhibitor

vWf, von Willebrand factor
Harrison MF. *West J Emerg Med.* 2018;19(5):863-871.

Coagulopathy in liver disease

- Rebalancing of hemostatic variables
  - Minimal effect on coagulation profiles despite presence of elevated INR
- Paradoxical phenomenon
  - Hypercoagulable state and elevated bleeding risk do not preclude each other
- Compensated and decompensated cirrhosis
  - Balanced hemostasis state or prothrombotic state
  - Factors II, IX, XI, and XII notably reduced
  - Serum levels of antithrombin, protein C, and protein S range 30-65% of normal
  - Chronic consumptive state of coagulants and anticoagulants
- Characterized by variable degree of decreased platelet count and function
  - Defective thromboxane A2 synthesis
  - vWf notably elevated

Rodríguez-Castro KI, et al. *World J Hepatol.* 2015;7(14):1818-1827

International Normalized Ratio (INR)

- Patients with cirrhosis often present with elevated INR values
- Assesses isolated clotting pathways in vitro
- Significant intrasubject variability
  - Differences of up to 0.7 depending on assay
- Guidelines established for procedures
  - Based on expert opinion
- Little evidence exists to support correlation with bleeding risk
- Best utilized to monitor degree of impairment or predict mortality
  - MELD score

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Risk of hemorrhagic events and mortality

- Six-fold increase in mortality from major and minor trauma in cirrhotic patients vs noncirrhotic controls
- MELD score correlates with mortality risk in trauma
  - Trauma-specific injury severity scores inadequate in cirrhotic trauma patients
- Higher trend of disseminated intravascular coagulation in cirrhotic patients vs noncirrhotic controls

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Risk of thrombotic events

- Portal vein thrombosis (PVT) commonly encountered despite elevated INR
  - 20-50% of patients with cirrhosis
  - May lead to intestinal infarction, ascites, or variceal bleeding
- False notion of "auto-anticoagulation"
  - Elevated INR does not protect against risk of venous thromboembolism (VTE) or PVT
  - Maintained capacity for thrombin generation or elevations in fibrinogen, factor VIII, and vWf
  - Risk for thrombosis increased by 6.3%
  - Greatest risk of thromboembolic events in patients with Child-Pugh Stage C
- Persistently present procoagulant factors

Harrison MF. *West J Emerg Med*. 2018;19(5):863-871.
Bergère M, et al. *Clin Res Hepatol Gastroenterol*. Published online ahead of print

Risk of thrombotic events continued

- Deep vein thrombosis (DVT) or pulmonary embolism (PE) occurs at rates of 4-12% despite prophylaxis in cirrhotic patients
- Relative risk for VTE >2
- VTE mortality rates increases with disease progression and higher Child-Pugh scores
- Serum albumin best predictor of VTE in cirrhotic patients
  - Surrogate for decreased protein synthesis by liver
- Prophylactic anticoagulation administered in only 21% of cirrhotic patients

Harrison MF. *West J Emerg Med*. 2018;19(5):863-871.

Laboratory assessment of hemostatics

- Thromboelastography (TEG)
  - Correlates well with in vivo clinical presentation
  - Performed in whole blood
  - Allows for consideration of multiple factors associated with coagulopathy
    - Rate of fibrin formation
    - Clot strength
    - Clot lysis
- Platelet count and function

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Management of coagulopathies

- Transfusion of fresh frozen plasma
  - Partial and transient correction
  - Fails to correct prothrombin time (PT) in 99% of patients
- Administration of vitamin K
- Blood product transfusions
- Cryoprecipitate
  - Increased risk of thrombotic events in end-stage liver disease (ESLD)
- Prophylactic anticoagulation for VTE

Harrison MF. *West J Emerg Med*. 2018;19(5):863-871.

Anticoagulation in cirrhosis

- Relative lack of experience in patient population
- VTE prophylaxis occurs in only 1 of 4 eligible patients with cirrhosis
- Use complicated by abnormal coagulation tests and presence of thrombocytopenia

Effects of cirrhosis on common coagulation tests			
Coagulation Levels	INR	aPTT	Anti-Xa
Effect of cirrhosis	Increased	Increased	Decreased

aPTT, activated partial thromboplastin time.
Ha NB, et al. *Ann Pharmacother*. 2016;50(5):402-409

Low-molecular-weight heparin (LMWH)

Advantages

- Safety profile
- Data available supporting long-term use for prophylaxis
- Rapidly reversible (relative)

Disadvantages

- Inconvenience and poor outpatient compliance
- Renal dose adjustments
- Effect on antithrombin
- Anti-Xa levels inaccurate in cirrhosis

Ha NB, et al. *Ann Pharmacother*. 2016;50(5):402-409

Unfractionated heparin (UFH)

Advantages

- Possible option in patients with renal dysfunction
- Rapidly reversible

Disadvantages

- Significant barriers to long-term use
- aPTT and anti-Xa levels inaccurate in cirrhosis

Ha NB, et al. *Ann Pharmacother*. 2016;50(5):402-409

Fondaparinux

Advantages

- Option for patients with history of heparin-induced thrombocytopenia

Disadvantages

- Unable to use in renal dysfunction
- Limited data exists

Ha NB, et al. *Ann Pharmacother*. 2016;50(5):402-409

Warfarin

Advantages

- Available via oral route
- Reversible effect

Disadvantages

- INR difficult to interpret in population
- Altered metabolism with liver dysfunction
- Drug and food interactions

Ha NB, et al. *Ann Pharmacother*. 2016;50(5):402-409

Direct oral anticoagulants (DOAC)

Advantages

- Limited monitoring necessary
- Available via oral route
- AUC for apixaban relatively unchanged in liver dysfunction (apixaban)

Disadvantages

- Lack of data
- AUC increased by 127% in moderate hepatic impairment (rivaroxaban)

Ha NB, et al. *Ann Pharmacother*. 2016;50(5):402-409
Hum J, et al. *Eur J Haematology*. 2017:98:393-397

Hum J, et al. 2017

- Retrospective cohort
- Evaluated outcomes of patients prescribed DOACs vs other anticoagulants
- Included patients prescribed DOAC, VKA, or LMWH
  - Indication for atrial fibrillation, DVT, or PVT
- Primary outcomes: bleeding events and recurrent thrombosis/stroke
- No differences in baseline characteristics
- 27 patients received DOAC, 18 patients received VKA/LMWH
  - Similar total bleeding events (p=0.12)
  - Fewer major bleeding events in DOAC group (1) vs others (5), p=0.03
  - No difference in rate of recurrent thrombosis

VKA, vitamin K antagonist.
Hum J, et al. *Eur J Haematol*. 2017;98:393-397

Loffredo L, et al. 2017

- Meta-analysis
- 8 studies
  - 7 cross-sectional studies
    - 2 prospective, 4 retrospective
  - 353 patients
- Evaluated the safety and efficacy of anticoagulation vs no anticoagulation in treatment of PVT
- LMWH or warfarin
- Anticoagulation associated with:
  - Higher recanalization rate (71% vs 42%): OR 4.8, 95% CI 2.7-8.7; p<0.0001
  - Lower incidence of PVT progression (9% vs 33%): OR 0.141; 95% CI 0.06-0.31; p<0.0001
  - No difference in major or minor bleeding (11% in both groups)
  - Lower rate of variceal bleeding (2% vs 12%): OR 0.232; 95% CI 0.06-0.94; p=0.04
- Duration had no effect on outcomes
- Only LMWH associated with complete PVT resolution

OR, odds ratio; CI, confidence interval.
Hum J, et al. *Eur J Haematol*. 2017;98:393-397

Villa E, et al. 2012

- Non-blinded, randomized controlled trial
  - Evaluators blinded to group assignments
- Primary endpoint: 2-year prevention of portal or mesenteric vein thrombosis
  - Secondary endpoints: occurrence/recurrence of liver decompensation, and overall and transplant-free survival
- Included eligible patients with Child-Pugh class B7-C10
- Randomized to enoxaparin 40 mg daily for 48 weeks or no treatment

Villa E, et al. *Gastroenterology*. 2012;143:1253-1260

Villa E, et al. 2012

- Enoxaparin-treated patients had:
  - Lower incidence of developed PVT
    - During treatment period (0% vs 16.6%, p=0.025)
    - At 2 years (0% vs 27.7%, p=0.001)
  - Decreased frequency of decompensation
    - During treatment period (11.7% vs 59.4%, p<0.0001)
  - Higher survival rate by Kaplan-Meier curve analysis (p=0.020)
- No difference in:
  - Frequency of decompensation at 2 years
  - Survival at 2 years
  - Bleeding episodes

Villa E, et al. *Gastroenterology*. 2012;143:1253-1260

Pharmacists post-test question #1

Which of the following statements are true?

a) PT/INR is an effective mean to assess bleeding risk in cirrhotic patients
b) Many patients with hepatic dysfunction are at a decreased risk of venous thromboembolism events due to auto-anticoagulation
c) Cirrhotic patients with Child-Pugh Stage C are at the greatest risk of thromboembolic events
d) Serum levels of protein C and S are elevated in patients with cirrhosis

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Pharmacists post-test question #2

All of the following are true regarding heparin and/or low-molecular-weight heparins (LMWH) in patients with cirrhosis EXCEPT:

a) Patients receiving anticoagulation are at a higher risk of major bleeding events than patients not receiving anticoagulation
b) Long-term enoxaparin use may significantly reduce the risk of liver decompensation
c) LMWH is the treatment of choice for the prevention and treatment of DVT/PE/PVT
d) All of the above are true

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Technician post-test question #1

All of the following statements are true in patients with cirrhosis EXCEPT:

a) Patients with cirrhosis are at an increased risk of venous thromboembolism when compared to noncirrhotic patients
b) Portal vein thrombosis is a common complication among patients with cirrhosis and may result in additional complications, including variceal bleeding
c) Cirrhotic patients experiencing minor or major trauma have been shown to have mortality rates six times that of non-cirrhotic patients.
d) PT/INR is an effective mean to assess bleeding risk in cirrhotic patients

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Technician post-test question #2

Which of the following is not recommended for treatment or prevention of venous thromboembolism in patients with cirrhosis?

a) Aspirin
b) Heparin
c) Enoxaparin
d) Apixaban

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References

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Questions?