Management of Disordered Hemostasis and Coagulation in Patients with Cirrhosis

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Introduction

The coagulopathy of cirrhosis and portal hypertension is complicated and often challenging to predict.[1,2] While patients with cirrhosis are clearly prone to bleed, there is often a concurrent paradoxical propensity toward thrombosis.[3] A finely regulated balance between bleeding and thrombosis is maintained in the healthy individual. When vascular breach or injury occurs, the clotting system activates (Fig. 1). In cirrhosis, a more precarious balance exists with heightened sensitivity to exogenous factors.[4-7] This rebalanced system is maintained by compensatory mechanisms, such as elevated levels of procoagulant factors like von Willebrand factor, FVIII, and reduced levels of anticoagulant factors like protein C.[4,5,7] Additionally, a fibrinolysis pathway (not shown) governs clot dissolution, which may be altered in cirrhosis. Factors like infection, renal dysfunction, and endothelial injury can alter this balance. Tests commonly used to predict bleeding such as the prothrombin time/international normalized ratio do not reliably predict bleeding risk in patients with cirrhosis.[8] Other, more global measures are currently under study and available in some centers (e.g., thromboelastography, thrombin generation assay), but there is no single test available today that can accurately predict bleeding or thrombosis tendency in patients with cirrhosis.

Management of the bleeding cirrhosis patient is well studied with established clinical guidelines.[9,10] Treating cirrhosis patients with thrombosis is less defined and clinicians must currently rely on expert recommendation, inference, and extrapolation from data in other patient populations.[11] As our understanding of the intricacies of the coagulation system in cirrhosis develops, new tests and treatments for thrombosis and bleeding will likely emerge.

The Bleeding Patient

The ultimate goal in caring for a patient with cirrhosis is to prevent bleeding before it occurs. Current recommendations effectively guide physicians treating portal hypertension–related bleeding.[10] Particular attention to the risk of overtransfusion is imperative, and practitioners should recognize the suggested target hemoglobin level (7-8 g/dL) when transfusing patients with cirrhosis.[9,12]

Procedural-related bleeding is a feared complication for the clinician caring for patients with cirrhosis. Without clear guidelines, clinicians are left to extrapolate approaches to care from other patient populations. There are several blood products and medications available for support of hemostasis (Table 1). Most procedures usually do not require routine prophylaxis (e.g., paracentesis, liver biopsy, most endoscopic procedures). At our institution, we routinely monitor levels of fibrinogen and platelets as a guide prior to major invasive procedures or to support hemostasis during active bleeding (Table 2). We advocate against routine use of fresh frozen plasma to correct the international normalized ratio in patients with cirrhosis, as it is often futile, increases portal pressures, and may cause transfusion-related injury. Rather, when necessary, we use cryoprecipitate to raise the fibrinogen level (goal: >120 mg/dL) and/or platelets transfused to a range of ~50-100 k/μL (depending on the type or invasiveness of the procedure and the clinical situation). Although more evidence is needed to support and guide clinical practice, we feel this is a rational approach based on current evidence and understanding of pathophysiology.

There are other agents available for prophylaxis and treatment of bleeding that have been studied in patients with cirrhosis. Routine use of recombinant factor VIIa is not currently recommended for prophylaxis in patients with cirrhosis but may have a role in rescue therapy.[10] The use of aminocaproic acid (an antifibrinolytic) topically after dental extraction is often effective in this patient population and used routinely in our center. Systemic administration for

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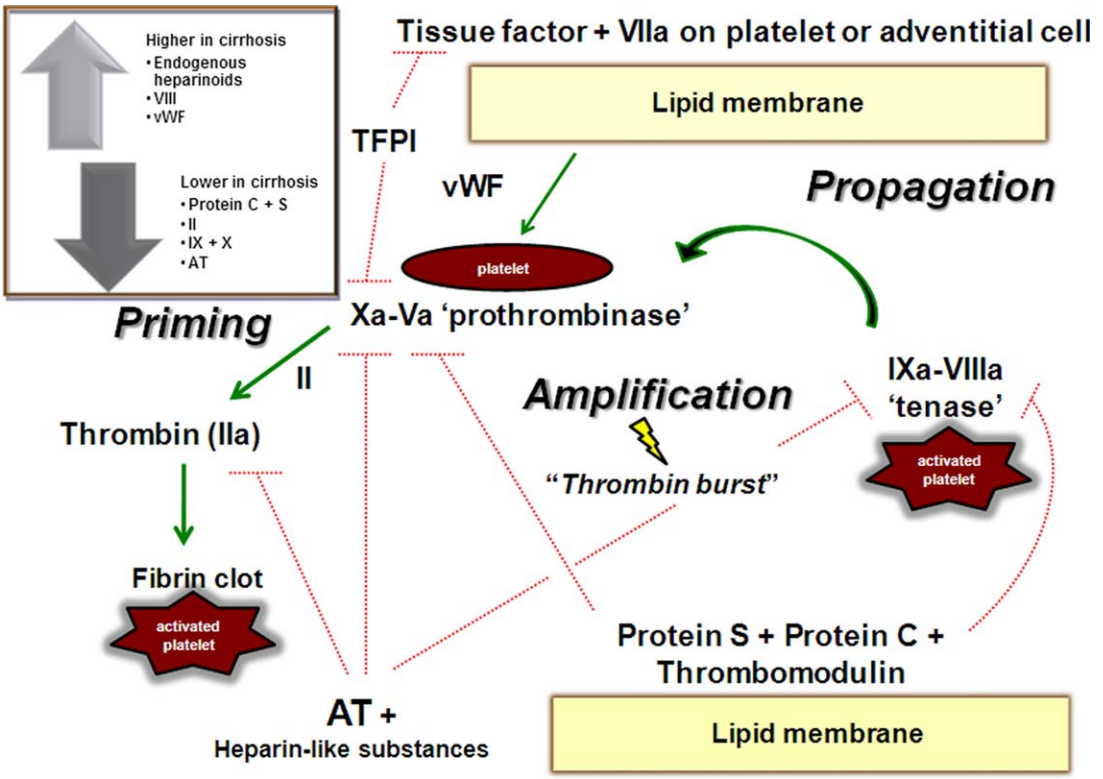

FIGURE 1 The coagulation cascade in normal conditions and the changes observed in cirrhosis (inset). Abbreviations: AT, antithrombin; TFPI, tissue factor pathway inhibitor; vWF, von Willebrand factor. Green lines indicate the pathway to generate of thrombosis (priming step, amplification, and propagation of thrombosis). Red lines indicate inhibition pathways. Reprinted with permission from *Hepatology* 2012;55:1634-1637. Copyright 2012, American Association for the Study of Liver Diseases.

TABLE 1 Therapeutics for Hemostasis

Therapeutic	Constituent	Mechanism	Pros	Cons
Fresh frozen plasma	All coagulation factors	Factor replacement	Widely available; contains all factors	Ineffective; requires large volume; risk of transfusion injury
Cryoprecipitate	Fibrinogen, FVIII, FXIII, fibronectin, von Willebrand factor	Factor replacement	Low volume; effective to replace fibrinogen	Risk of transfusion injury
Prothrombin complex concentrates	FII, FVII, FIX, FX, protein C + S	Factor replacement	Concentrated; studied in liver disease	Not widely available; expensive; risk of thrombosis
Recombinant FVIIa	FVII	Factor replacement	Concentrated; studied in liver disease	Expensive; unclear efficacy; risk of thrombosis
Platelets	Donor-pooled platelets	Initiation of primary hemostasis; propagation of coagulation cascade and enhancement of thrombin generation	Provides essential component of coagulation cascade	Risk of transfusion injury
Vitamin K	Oral or intravenous formulations	Promotes synthesis of FII, FVII, FIX, FX, protein C+S	Inexpensive; available	Unclear efficacy; hypersensitivity reactions
Desmopressin	Intranasal or intravenous formulations	Increases production of FVIII + von Willebrand factor, enhancing platelet adherence	Available; relatively safe; studied in liver disease	Unclear efficacy; tachyphylaxis occurs with repeated use
Antifibrinolytics*	Intravenous formulations with loading doses; can use topically	Disrupts interactions between plasminogen/plasmin and fibrin	Studied in liver disease; also effective topically for mucosal oozing (e.g., dental extractions)	May have risk of thrombosis; not-well studied in liver disease; lack markers/tests of hyperfibrinolysis

*Aminocaproic acid, tranexamic acid, aprotin. (Aprotin has been removed from the market due to thrombosis and mortality risks.)

TABLE 2 Approach to Procedural-Related Bleeding, Prophylaxis, and Rescue Therapy in Patients with Liver Disease*

1. **Identify the risk of procedure and clinical situation:**
   - Assess patient's bleeding history and carefully examine for physical clues (i.e., ecchymosis, epistaxis, or other mucosal bleeding)
   - Determine whether prophylaxis is necessary, realizing that most routine procedures (e.g., esophagogastroduodenoscopy with band ligation, colonoscopy with polypectomy, large volume paracentesis, liver biopsy,* hepatocellular carcinoma local-regional therapy) do not require routine prophylaxis
   - In cases of active bleeding, once initial resuscitation occurs, avoid immediate volume expansion with unnecessary blood products or fluid

2. **Optimize the patient prior to procedure:**
   - Ensure that appropriate medical therapy is administered (i.e., antiportal hypertensive therapy in some conditions)
   - Correct platelet count >50,000 k/μL if evidence of ongoing bleeding or high-risk procedure
   - Correct fibrinogen level >120 mg/dL (with cryoprecipitate) if evidence of ongoing bleeding or high-risk procedure
   - Avoid overtransfusion of blood and optimize renal function
   - Avoid using international normalized ratio as a barometer of bleeding risk and do not use fresh frozen plasma to attempt to correct it
     - Vitamin K replacement can be occasionally helpful in malnourished patients
   - Consider preprocedure prophylactic use of desmopressin (intranasal preparation) as an adjunct for patients with uremia

3. **Preplan rescue therapies in case of complication:**
   - Arrange backup with interventional radiology if indicated (i.e., need for transjugular intrahepatic portosystemic shunt, hepatic angiogram)
   - Consider use of alternative agents like recombinant FVIIa, prothrombin complex concentrates or aminocaproic acid in special circumstances

4. **Recognize the retained risk of hypercoagulability in cirrhosis patients and unintended thrombotic complications these therapies may have even if patient demonstrates bleeding**

*We do not routinely use prophylaxis in cirrhosis patients prior to esophagogastroduodenoscopy with banding, large volume paracentesis, or colonoscopy. Each clinical situation may require special consideration.
†Prior to percutaneous liver biopsy, we follow the approach detailed in the American Association for the Study of Liver Diseases guidelines and favor preprocedure blood work and imaging.[21] As with other solid organ biopsy in this setting, we would aim to optimize platelets and fibrinogen and consider use of adjuncts such as desmopressin while avoiding attempts at "correcting" the international normalized ratio with plasma for reasons reviewed in text (poor target and side effects of volume expansion).

TABLE 3 Therapeutics for Thrombosis

Therapeutic	Route	Mechanism of Action	Pros	Cons
Unfractionated heparin	IV or SC injection	Potentiates antithrombin, inactivating thrombin, Fxa	Clear monitoring parameters; can use with renal insufficiency	Requires three times daily dosing in SC form for prophylaxis; unclear efficacy; not well-studied in cirrhosis
Low molecular weight heparin (enoxaparin, dalteparin, nadroparin)	SC injection	Potentiates antithrombin, inactivating thrombin, Fxa	Most extensively studied class of anticoagulants in cirrhosis patients	Affected by renal insufficiency; SC route can cause complications; patient intolerability and adherence issues
Vitamin K antagonist (warfarin)	Oral	Inhibits vitamin K epoxide reductase complex, reducing synthesis of FII, VII, IX, X, protein C+S	Inexpensive; studied in cirrhosis patients; reversible with antidote	Difficult to monitor using international normalized ratio in cirrhosis patients; requires frequent monitoring
Factor Xa inhibitors (fondaprinux, rivaroxaban, apixaban)	SC injection Oral Oral	Directly inhibit FXa	Oral administration	Not studied in cirrhosis patients; unclear dosing parameters, monitoring parameters, and efficacy
Direct thrombin inhibitor (dabigatran)	Oral	Directly inhibits thrombin, preventing thrombin-mediated effects	Oral administration	Not studied in cirrhosis patients; unclear dosing parameters, monitoring parameters, and efficacy
Aspirin	Oral	Irreversibly inhibits platelet aggregation	Not well-studied in cirrhosis	Can cause fluid retention and renal dysfunction; unclear efficacy in setting of thrombocytopenia/thrombocytopathia
Inferior vena cava filter	NA	Mechanical prevention of embolic event	May prevent pulmonary embolism	Not studied in cirrhosis; thrombotic nidus; can interfere with future transplantation; unclear efficacy
Direct thrombolysis	NA	Local infusion of tissue plasminogen activator	Useful for select cases of splanchnic thrombosis	May require subsequent anticoagulation and/or transjugular intrahepatic portosystemic shunt to decreases stasis in cases of portal vein thrombosis

Abbreviations: IV, intravenous; NA, not applicable; SC, subcutaneous.

patients exhibiting clinical signs of hyperfibrinolysis (delayed mucosal or puncture site bleeding) should also be considered in select cases. Other therapies—such as desmopressin, vitamin K for malnourished patients, and prothrombin complex concentrates—offer potential adjunct therapies, which can be considered for prophylaxis or treatment of active bleeding.

The Clotting Patient

There is emerging evidence that prevention of venous thromboembolism and portal vein thrombosis is a safe and effective strategy in patients with cirrhosis.[13-15] A recent prospective study in outpatient cirrhosis patients demonstrated that therapy with prophylactic dosing of a low molecular weight heparin decreased formation of portal vein thrombosis, reduced decompensation events, and improved survival.[15] Further studies are necessary in larger populations to corroborate these important findings. In an effort to prevent peripheral venous thrombosis during hospitalizations, medical prophylaxis should be considered in cirrhosis patients without contraindications.

Clinical signs of thrombosis are often subtle, hence clinicians who care for patients with cirrhosis should exercise persistent suspicion. Once thrombosis is established, the decision to treat may provoke considerable apprehension. Moreover, there are now numerous available anticoagulants compounding the complexity of treatment decisions (Table 3). There are no current guidelines to provide direction to clinicians, as most clinical trials exclude patients with cirrhosis. Eradication of esophageal varices via band ligation is recommended prior to initiating any long-term anticoagulation. Furthermore, use of nonselective beta-blockers is recommended if varices are present to reduce risk of bleeding. Low molecular weight heparin and warfarin are the most widely studied anticoagulants for treatment of portal vein thrombosis in patients with cirrhosis.[16-20] New oral therapies offer great promise, but use is currently limited due to lack of knowledge regarding pharmacodynamics, safety, and efficacy.

Conclusions

Over the last decade, a remarkable paradigm shift in the approach to the coagulopathy of cirrhosis has occurred. It is perplexing to care for patients who profusely hemorrhage from an acute esophageal variceal bleed one day, only to discover an acute venous thrombus soon thereafter. However, this paradox is not so rare as once perceived. Predicting tendencies to bleed or clot and developing strategies to prevent these complications is the ultimate goal of study in this field and will inevitably lead to improved outcomes.

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