ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation (Part 1 of 2)

By Hima Veeramachaneni, MD

@EmoryGastroHep

General Considerations

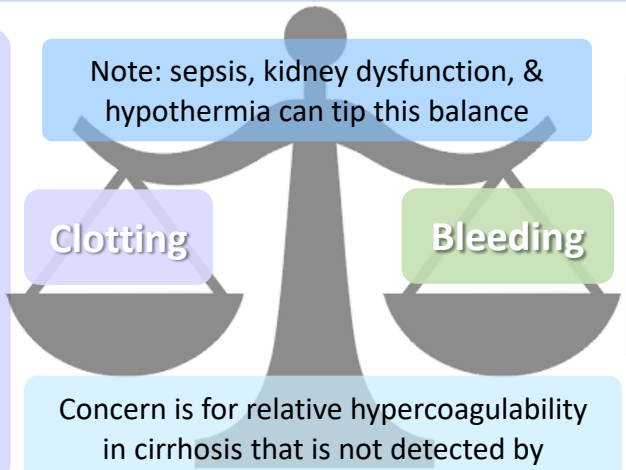
- Hemostasis involves multiple systems: liver, platelets, & endothelium
- Role of liver:
  1) Produce coagulation factors & coagulation inhibitors
  2) Clear factors by synthesizing plasminogen
  3) Produce TPO (thrombopoietin) to stimulate bone marrow to produce platelets
- Hemostatic pathways in compensated cirrhosis are mostly intact
- Bleeding in cirrhosis is not always related to coagulation cascade homeostasis
- Some common bleeding in cirrhosis can be related to portal pressure or acute illness

Defects observed in cirrhosis

↑ Levels of vWF & factor VIII

↓ Protein C, protein S, & antithrombin

↓ Plasminogen



Defects observed in cirrhosis

Thrombocytopenia

↓ Factor levels (II, V, VII, IX, X, & XI)

Assessment of bleeding risk

- INR correlates poorly with thrombin generation & risk of bleeding in cirrhosis
- Whole blood viscoelastic tests, thromboelastography, & rotational thromboelastometry are a better measure of the viscosity/fibrin clot & may be useful in patients with ↑ INR BUT more studies needed with these tests

Platelets in Cirrhosis

Thrombocytopenia is multifactorial:
- Mainly due to hypersplenism & platelet sequestration
- Other contributing factors: ↓ hepatic TPO production & functional impairment of platelets

TPO-receptor agonists: help stimulate thrombopoiesis & decrease need for platelet transfusions for procedures BUT have ↑ risk of thromboembolic events, especially PVT

Platelets <50,000/mL: Transfusion is **not** recommended for routine procedures (variceal banding or paracentesis) BUT is appropriate for high-risk procedures

Hypercoagulability in Cirrhosis

- Activated hemostatic pathways → small vessel thrombosis & organ atrophy
- In-hospital DVT prophylaxis: safe if not bleeding & platelets >50,000/mL
- PVT & DVT are common in cirrhosis → treatment consideration should include degree of thrombosis, presence of associated symptoms, relative fall risk, & variceal bleeding risk

Bleeding in Cirrhosis

Categorized broadly into 3 categories:
1) Portal hypertensive related bleeding due to ↑ portal pressure
2) Mucosal/wound bleeding due to hemostatic defects
3) Delayed postprocedural bleeding and mucosal or puncture wound oozing due to accelerated intravascular coagulation and fibrinolysis (AICF)

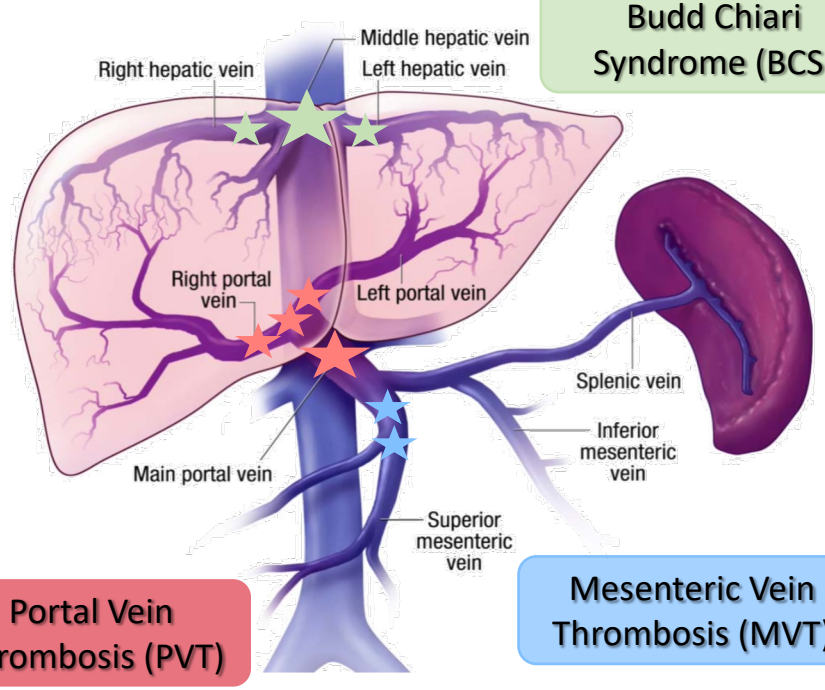
Fibrinogen: Can have ↓ fibrinogen levels with ↑ fibrin/fibrinogen degradation products
- Transfuse for fibrinogen levels >120-150 for high-risk procedures
- Fibrinolytic agents: only recommended if hyperfibrinolysis is present in active bleeding

↑ INR: Prophylactic infusion of ≥2 units of FFP is **not** recommended (leads to ↑ portal pressure → ↑ risk of bleeding)

Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol. 2020 Jan 3; 115(1): 18-40. doi: 10.14309/ajg.0000000000000486

Diagnosis of PVT/BCS/MVT

- US doppler should be initial screening modality
- Contrasted CT or MRI should be used to assess extension of thrombus, determine acuity, exclude tumor, confirm diagnosis if unclear on US, and/or assess response to therapy (in some cases)
- Contrasted CT imaging can have >90% accuracy



Budd Chiari Syndrome (BCS)

Portal Vein Thrombosis (PVT)

Mesenteric Vein Thrombosis (MVT)

Patients with PVT + cirrhosis + portal hypertension sequelae can also be considered for TIPS placement (in incomplete occlusion) or transhepatic/ transsplenic approach (in complete occlusion)

*Treating esophageal varices decreases risk of bleeding when starting anticoagulation

Portal Vein Thrombosis

- Presents as acute upper abdominal pain and fever raises suspicion for PVT
- If new fever, ascites, rebound abdominal tenderness, ↑ WBC, ↑ lactate → suspect intestinal ischemia

Without Cirrhosis

- **Workup:** thrombophilia workup if no other acute intraabdominal process to explain
- 25% are due to myeloproliferative disorders

Cirrhosis

- Prevalence: 1-20%
- No data to support prophylaxis against PVT
- Cirrhosis is an independent risk factor for PVT
- **Workup:** thrombophilia workup if

1) Prior history of thrombosis
2) Thrombosis of unusual sites
3) Family history thrombosis

Acute

Chronic

Bland

Tumor

Bowel ischemia

Thrombus progression
MV extension
Thrombophilia

Acute

Partial

Complete

EGD

Large varices

No/Small varices

Non-selective BB or band ligation*

If liver transplant candidate

Initiate Anticoagulation

Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol. 2020 Jan 3; 115(1): 18-40. doi: 10.14309/ajg.0000000000000486

Causes of PVT/MVT

Local factors with injury to portal or mesenteric veins

- Acute intraabdominal process: pancreatitis, IBD, diverticulitis, cholecystitis, appendicitis
- Intraabdominal surgery: cholecystectomy, colectomy, liver transplant, splenectomy, TIPS
- Abdominal trauma

Thrombophilia

- Malignancy: intraabdominal, myeloproliferative, HCC
- Paroxysmal nocturnal hemoglobinuria
- Other inherited/genetic thrombophilia conditions
- ↑ estrogen: pregnancy, OCP

Sluggish blood flow: Cirrhosis or HF

Mesenteric Vein Thrombosis

- Can be an extension of PVT
- MVT contributes to 10-20% of ischemic disorders
- Most common presentation: abdominal pain, nausea/vomiting, fever, anorexia, & jaundice
- Treating acute symptomatic MVT with anticoagulation→ prevention of bowel ischemia, reduced hospitalization, & improved survival
- Thrombolytic therapy can be considered in progressive thrombus
- Those with intestinal infarction → require surgical resection

Portal Hypertensive Cholangiopathy

- Portosystemic collaterals can lead to CBD obstruction
- **Prevalence**: 0.5-1% of patients with chronic PVT
- **Diagnosis**: cholestatic liver chemistry profile, portal cavernoma, & MRCP with extrahepatic biliary abnormalities
- **Treatment**: endoscopic intervention with stone removal/biliary stent placement

Considerations with Anticoagulation

Goal: decrease clot propagation & restore patency of the portal or mesenteric vein

Duration

Discrete precipitant: At least 6 months

Thrombophilia or liver transplant candidate: indefinite

Considerations

Weigh benefits/risks based on patient characteristics (i.e., plts <50k or HE with risk of falls)

Initiating Anticoagulation

	Unfractionated heparin	LMWH
Administration	IV	SQ
Frequency	Infusion	BID
Half-life	Minutes to 1-2 hours	6-12 hours
Monitoring	aPTT or Xa	Not needed
Renal function	No dose adjustment	Contraindicated in renal failure
Efficacy	++	+++
Heparin-induced thrombocytopenia	+++	++

Maintaining Anticoagulation

	LMWH	VKA	DOAC
Administration	SQ	Oral	
Frequency	BID	Daily	
Efficacy	Better in cancer	++	
Renal function	Contraindicated in renal failure	No dose adjustment	
Absorption	Not affected	Affected from bowel edema in portal hypertension (may consider monitoring of therapy)	
Monitoring	Not needed	Needed with PT/ INR	Probably not needed
Antidote	Available		

Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol. 2020 Jan 3; 115(1): 18-40. doi: 10.14309/ajg.0000000000000486

ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation (Part 2 of 2)

By Hima Veeramachaneni, MD

Budd Chiari Syndrome

Diagnosis

- Primary: Thrombotic obstruction of hepatic venous outflow tract
- Secondary: malignant tumors or extrinsic compression of hepatic veins
- Diagnosis: Imaging- US doppler, CT, & MRI are comparable; US doppler= most cost effective and recommended initial test
  - Hepatic venogram and liver biopsy are rarely needed for diagnosis
- Workup: acquired/ inherited thrombotic conditions & referral to hematologist
  - 79-84% of patients with ≥1 thrombotic disorder
  - 25-46% of patients with ≥2 thrombotic disorders

Clinical Manifestations

- Initial presentation: ascites, abdominal pain, elevated liver enzymes
- Most commonly a subacute to chronic hepatic venous outflow obstruction but can have fulminant liver failure
- Complications related to portal hypertension

Causes

Thrombophilia

Acquired	Inherited
• Myeloproliferative disease (~50% of cases) • Polycythemia vera • Essential thrombocytosis • Idiopathic myelofibrosis • JAK2 mutation • Paroxysmal nocturnal hemoglobinuria • Behcet's disease • Hyperhomocysteinemia • Antiphospholipid syndrome	• Factor V Leiden • Mutations: prothrombin gene, methyltetrahydrofolate C677T • Thalassemia • Deficiencies: protein C or S, antithrombin

Systemic Factors

- Sarcoidosis
- Vasculitis
- Behcet's disease
- Connective tissue disease
- Inflammatory bowel disease

Hormonal factors

- Recent OCP use
- Pregnancy

Management

Prognostic scoring systems are not helpful for guiding choice of therapy

- 1st line= **anticoagulation** → acute: heparin/LMWH, chronic: warfarin
- Hematology referral for consideration of therapies for underlying conditions
- Worsening liver +/- renal function, ascites, or HE → **angioplasty or TIPS**
- If complete hepatic vein obstruction → ultrasound guided direct intrahepatic portosystemic shunt (**DIPS**) to connect portal vein & IVC
- Short segment hepatic vein stenosis → **balloon angioplasty of hepatic vein +/- stent**
- If DIPS or TIPS not feasible → **portosystemic shunt surgery**
- TIPS failure or fulminant liver failure → **liver transplant** (10-15% of patients)
- **HCC surveillance**: chronic BCS → q6 month US abdomen + AFP (If nodule present, need CT/MRI for further evaluation)

Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol. 2020 Jan 3; 115(1): 18-40. doi: 10.14309/ajg.0000000000000486

Mesenteric Artery Aneurysms

Demographics

- Usually present after the 6th decade of life
- Most common= splenic artery aneurysms (60%)→ more common in multiparous women
- 2nd most common= hepatic artery aneurysm
- 1/3 of patients have multiple aneurysms
- Can be true aneurysms or pseudoaneurysms
- Usually incidentally found on imaging

Management

- Treat with endovascular stents, coiling, or embolization if:
  1) Associated with symptoms
  2) Pseudoaneurysms associated with acute pancreatitis
  3) >2cm in diameter
  4) Asymptomatic but
  - Women of childbearing age
  - Aneurysm of pancreaticoduodenal and gastroduodenal arcade or intraparenchymal hepatic artery branches
  - Liver transplant recipient
- If not meeting above criteria → surveillance @6 months → @1 year→ then every 1-2 years

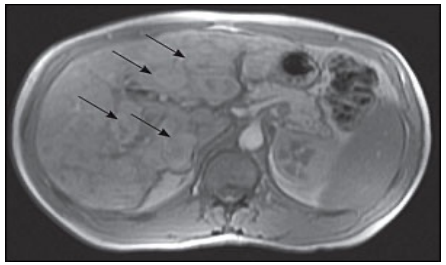
Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol. 2020 Jan 3; 115(1): 18-40. doi: 10.14309/ajg.0000000000000486

Hereditary Hemorrhagic Telangiectasia (HHT, Osler-Weber-Rendu Disease)

- Genetic disorder → autosomal dominant mutation of gene effecting protein in vascular endothelium
- Widespread cutaneous, mucosal, and visceral telangiectasias
- Affects 1 in 5,000-8,000 people
- 55% have **liver vascular malformations (LVMs)** with 3 types of shunting with associated complications:

1) Hepatic artery to hepatic vein (most common) → high-output heart failure (HOHF), ischemic cholangiopathy with secondary sclerosing cholangitis, bilomas
2) Hepatic artery to portal vein → portal hypertension (PH) 2' to nodular regenerative hyperplasia (NRH)
3) Portal vein to hepatic vein → portosystemic encephalopathy (PSE), HOHF

**Mesenteric ischemia is a potential complication due to hepatic artery steal from mesenteric vessels



https://www.aafp.org/afp/2010/1001/p785.html

LVM Diagnosis

- No routine screening for LVMs
- Screen with CTA or MRA if
  - Liver bruit or palpable thrill
  - Hyperdynamic circulation
  - Abnormal liver tests
- Imaging findings (in CT above):
  - Intrahepatic hypervascularization
  - Enlarged hepatic artery
- Liver biopsy & angiography not recommended

LVM Management

- Asymptomatic LVMs = no treatment
- Standard treatment = symptomatic management
  - HOHF → sodium restriction, diuretics, beta blocker, pregnant patients should have expedited delivery
  - PH → treatment of ascites, varices, PSE. TIPS doesn't fix potential of bleeding
  - Secondary sclerosing cholangitis → ursodeoxycholic acid
  - Bilomas → analgesics if pain, drainage & antibiotics if infected
- Targeted therapy considerations (evidence limited)
  - **Bevacizumab** = antibody against vascular endothelial growth factor → try 1st since least invasive, especially for HOHF
  - **Hepatic artery occlusion** with surgical ligation or embolization for PH or biliary involvement → high morbidity/mortality due to biliary +/- hepatic necrosis
  - **Liver transplantation** → high perioperative complications, LVMs can recur as early as 6 years after transplant