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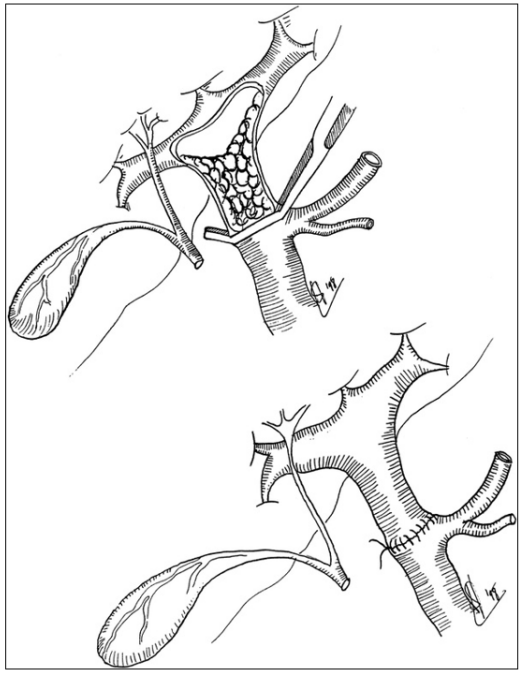
Vascular Disorders of the Adult Liver



Yerdel et al. Transplantation 2000

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- I have no other relevant disclosures pertinent to this presentation
- I will be discussing off-label usage of medications

Outline

1. Overview of liver anatomy and the mesenteric vascular system
2. Coagulation in liver disease: A modern perspective
3. Management of coagulopathy and bleeding in liver disease
4. Portal vein thrombosis
5. Hepatic vein thrombosis (Budd-Chiari syndrome)
6. Idiopathic non-cirrhotic portal hypertension
7. Sinusoidal Obstruction Syndrome (SOS) / Veno-occlusive Disease (VOD)
8. Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu syndrome) and Liver Vascular Malformations (LVMs)
9. Hepatic and splenic artery aneurysms

The Liver and Mesenteric Circulation

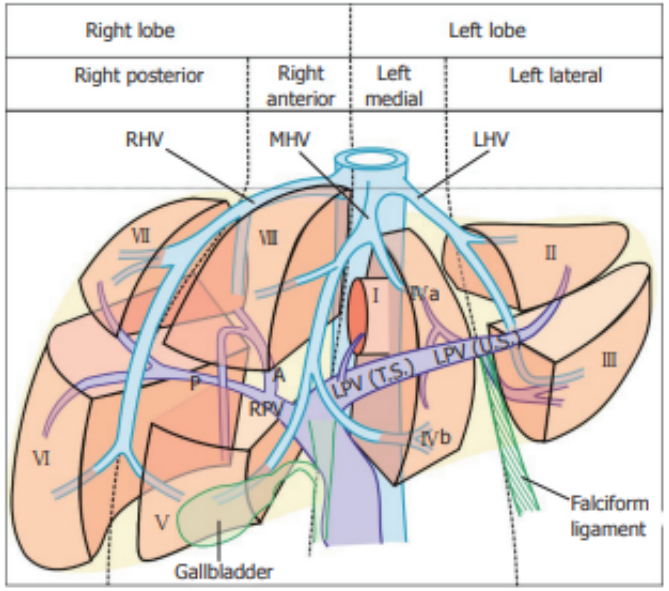


Figure 1 Three vertical planes and a transverse plane divide the liver into four sectors and eight segments. The vertical planes divide the liver into four sectors. The transverse plane divides the liver into superior and inferior segments. LHV: Left hepatic vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LPV: Left branch of the portal vein; RPV: Right branch of the portal vein.

Sharma et al.
World J Gastrointest Endosc 2018

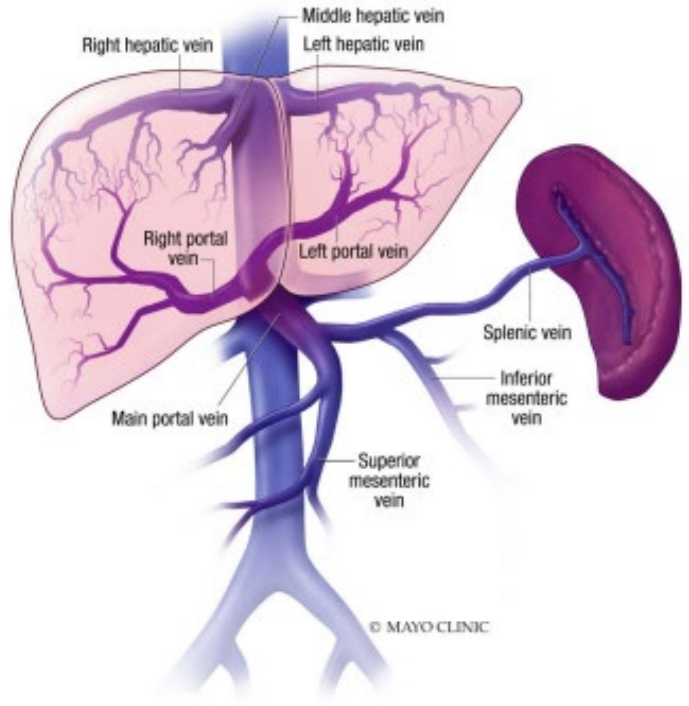
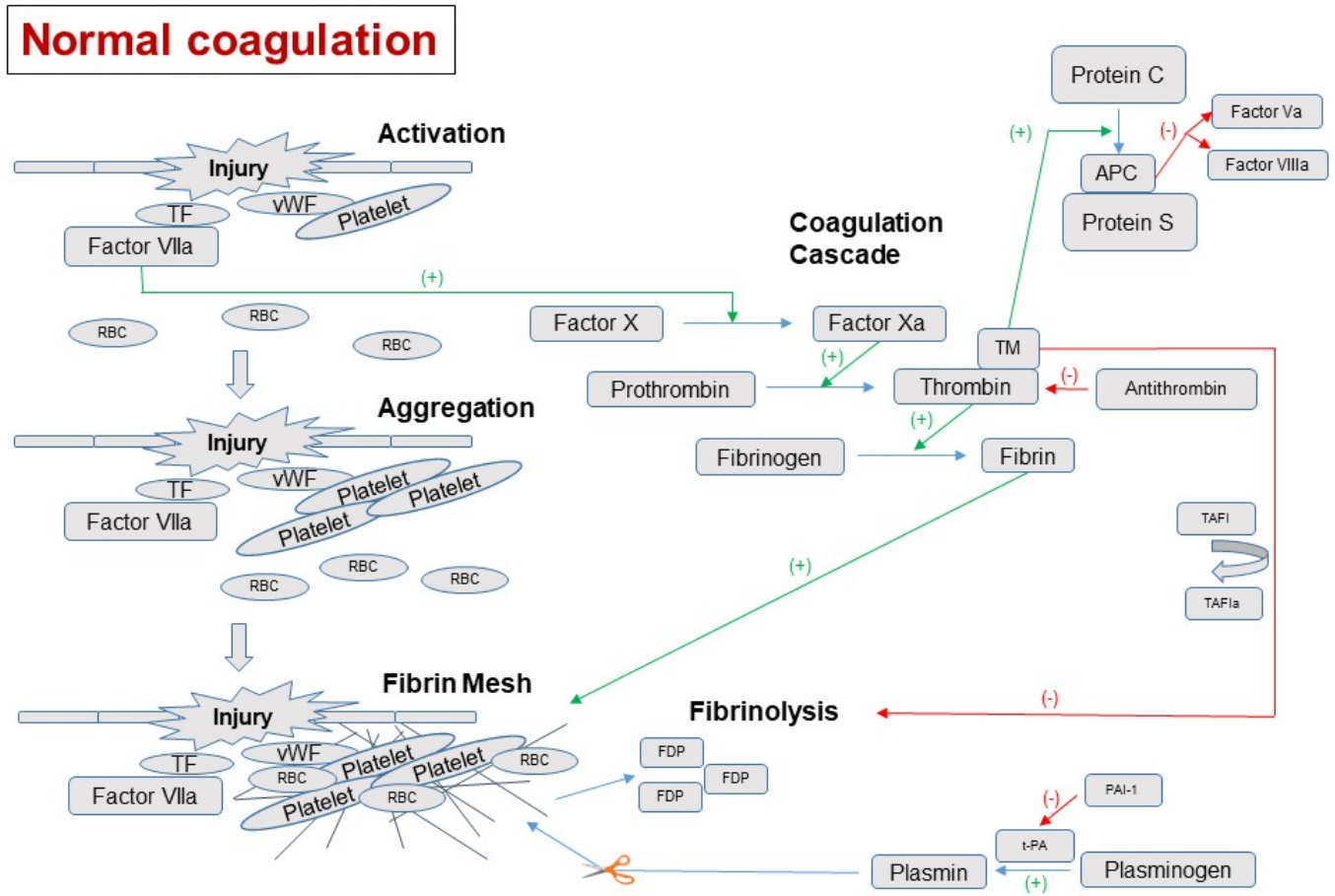


Figure 1. Hepatic and portal venous system.

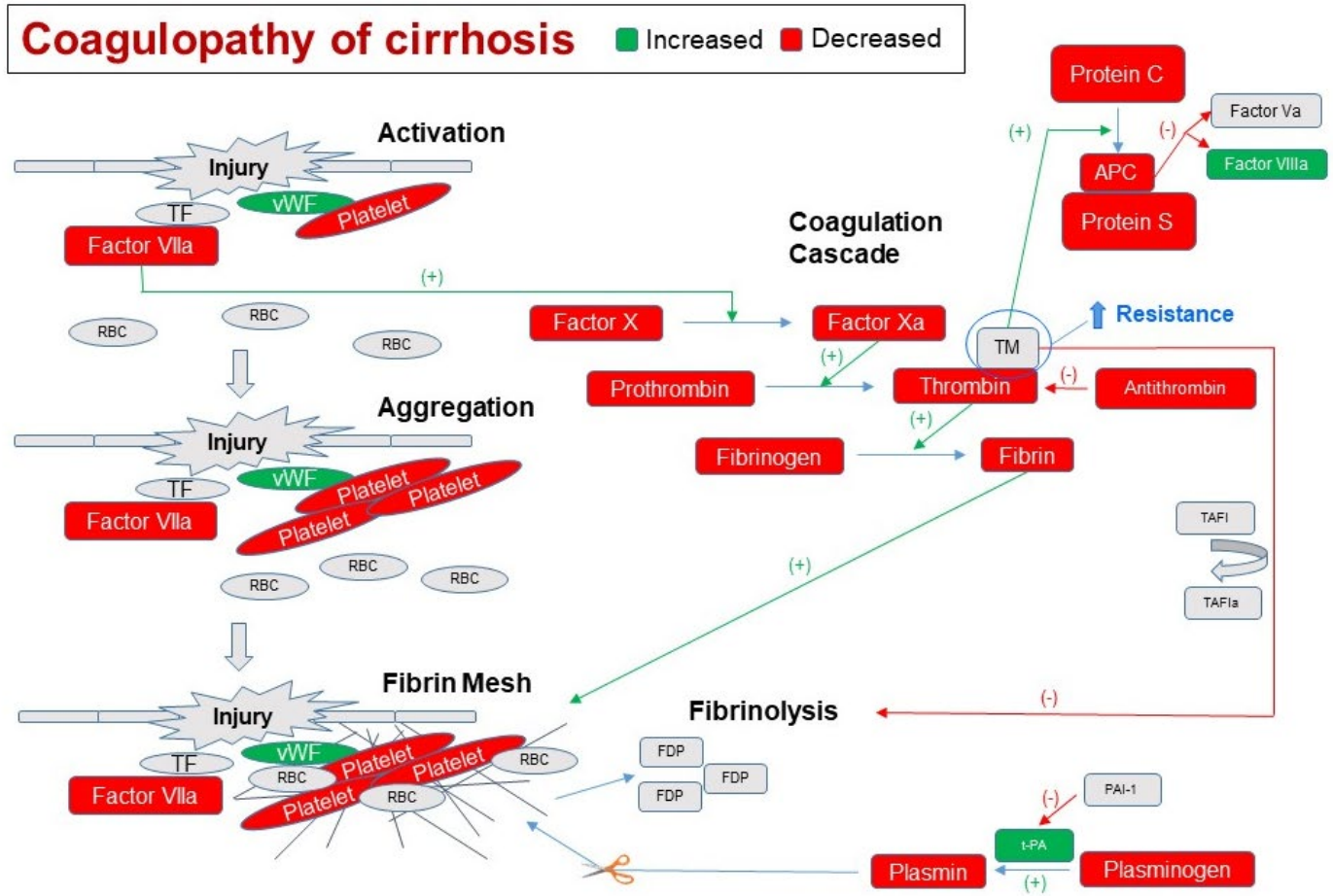
Simonetto et al. Am J Gastroenterol 2020

Normal Coagulation



Wentworth et al. "Hematological Conditions and the Liver." INEDSYS Hepatology: A Comprehensive Textbook, Satapathy et al. (Ed), McGraw Hill, *In Press*.

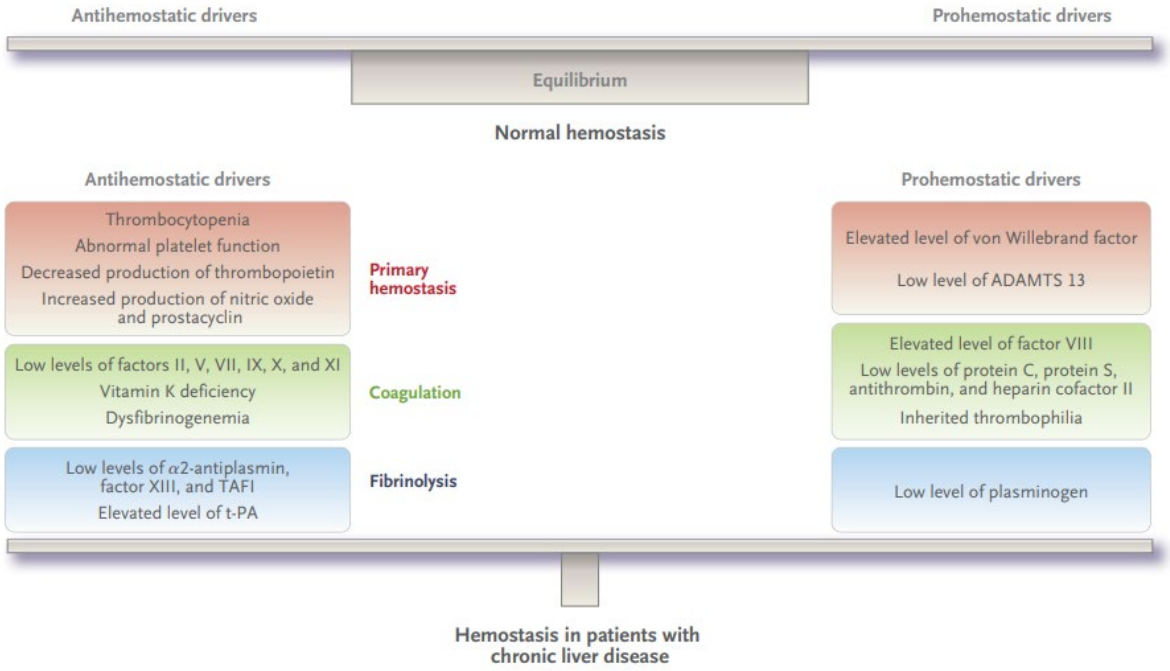
Coagulation in liver disease: An overview



Wentworth et al. "Hematological Conditions and the Liver." INEDSYS Hepatology: A Comprehensive Textbook, Satapathy et al. (Ed), McGraw Hill, *In Press*.

Coagulation in liver disease: Key points

- "Rebalanced" but unstable
- Traditional markers of coagulation (platelets, INR) are unreliable
- Platelet level between 50-60 x 10^9 / L necessary for adequate thrombin generation
- Use of viscoelastic testing: thromboelastography [TEG] and rotational thromboelastometry [ROTEM] are of increasing interest
    - Routine clinical use outside of perioperative transfusion guidance in liver transplantation remains limited
    - Isolate specific coagulation defects to determine optimal product selection



Tripodi and Mannucci. N Engl J Med 2011

Tripodi et al. Hepatology 2006; Davis et al. Ann Hepatol 2018

Management of Coagulopathy in Liver Disease

Clinical issue	Successful coagulation management opportunity	Potential pitfalls
Bleeding esophageal varices	Rapid endoscopic and medical therapy should be applied Transfuse platelet concentrates with target of at least 56×10^9/L Maintain fibrinogen >100 mg/dL with cryoprecipitate Goal should be to resuscitate as needed but avoid increase in portal pressure	Avoid overtransfusion with packed red blood cells, aim for target hemoglobin or 7 g/dL Avoid use of empiric FFP unless clear indications are evident
Performance of invasive procedures	Weigh the risks of severe procedural bleeding (and the ability to stop it) against the need for prophylaxis If high-risk procedure, transfuse prophylactic platelets to a target of at least 50–60 $\times 10^9$/L or closer to 100 $\times 10^9$/L for very high risk If postprocedural bleeding occurs in mucosal sites or from puncture wounds, consider hyperfibrinolysis Treat underlying disorders aggressively before elective procedures (infection, renal failure, etc) Intranasal DDAVP may be an effective and economical alternative prophylactic measure in procedures such as dental extractions	Do not use a moderately elevated INR (<3) as a measure of procedural bleeding risk Avoid using FFP for prophylaxis, but if used, recall that adequate dosing to replace factors is 20–40 mL/kg rFVIIa should be avoided for prophylaxis in all but the highest-risk procedures
ALF	Despite highly abnormal traditional coagulation indexes, most ALF patients have reached a whole body hemostatic balance A single dose of rFVIIa (40 μg/kg) can facilitate performance of intracranial pressure monitor placement in ALF patients	Do not use prophylactic transfusion of FFP or platelets in ALF without clinically evident bleeding Do not use continuous infusions of rFVIIa in ALF patients because of the potential for thrombotic complications and high cost

rFVIIa, recombinant activated factor VII.

Northup PG and Caldwell SH. Clin Gastroenterol Hepatol 2013

- pRBC over-transfusion and FFP use → raises portal pressures, worse outcomes
- Routine plt transfusion for variceal hemorrhage, paracentesis, thoracentesis, liver biopsy, dental extractions is not recommended
    - Alt: TJ biopsy; intranasal DDAVP and adjunctive aminocaproic-acid soaked gauze for dental extractions
- Routine vitamin K non-beneficial unless treating VKA-induced coagulopathy or vitamin K deficiency
- Limited evidence for rFVIIa outside of intracranial pressure monitor placement
- Limited evidence/utility of 4-factor prothrombin complex concentrate
- Adjunctive aminocaproic acid or tranexamic acid for non-portal pressure-related bleeding can be considered

Mohanty et al. Liver Int 2021; Garcia-Tsao et al. Hepatology 2017

Portal Vein Thrombosis

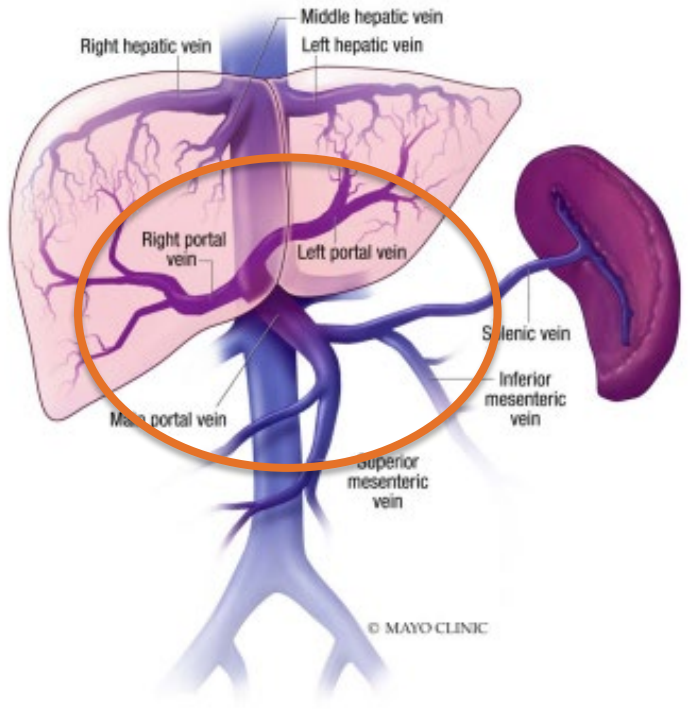
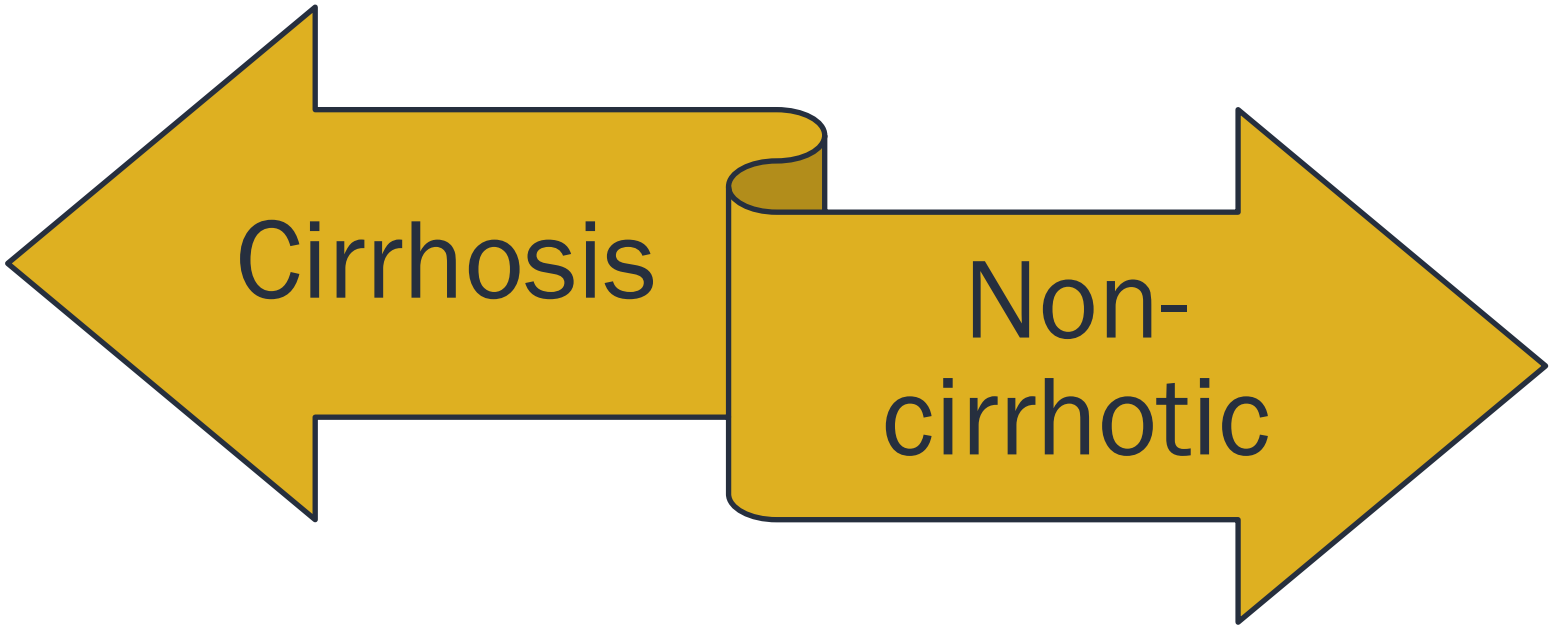


Figure 1. Hepatic and portal venous system.

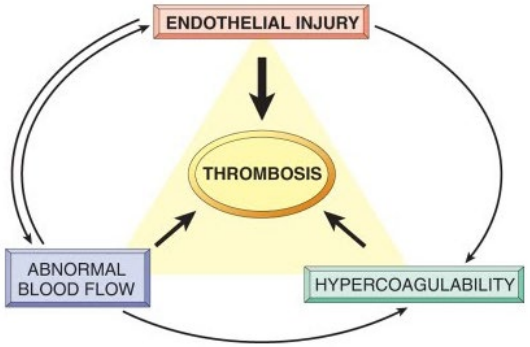
Portal Vein Thrombosis: A Framework

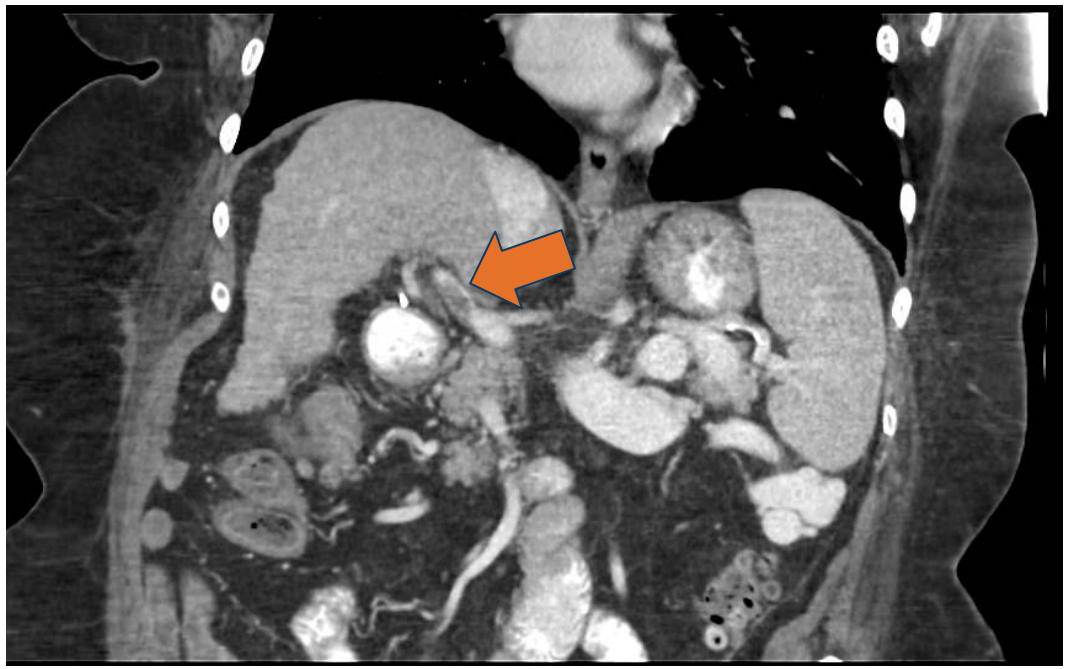
- **Who?** *Patient characteristics*
- **What?** *Symptoms*
- **When?** *Acuity and transplant eligibility?*
- **Where?** *Location/extent of involvement*
- **Why?** *Provoked or underlying thrombophilia?*

PVT: Who?



PVT in Cirrhosis: An overview



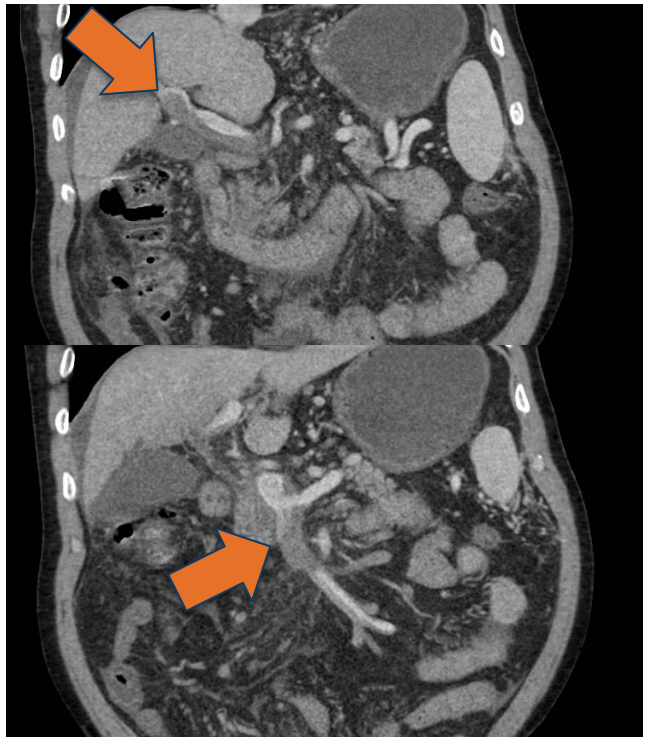


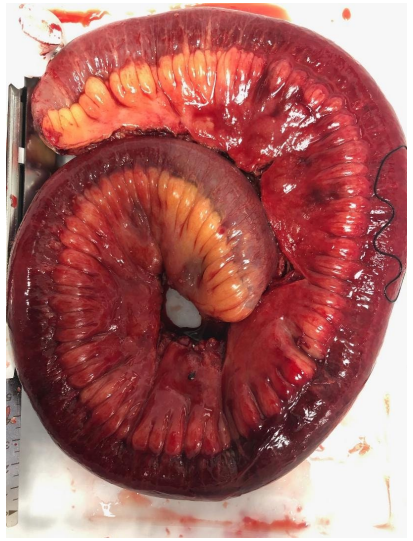
- Common
  - Prevalence: 2-26%
  - Incidence: 3.7-4.6% annually
- Risk factors: decompensated disease, malignancy (HCC), PV velocity <15cm/s, NASH
- Unclear if associated with disease progression and/or mortality – literature is conflicting
  - In LT recipients, PVT associated with increased post-transplant mortality
- Complicates transplant – non-anatomical PV reconstruction
- Underlying thrombophilia uncommon – testing not recommended unless FH and/or hx of other thrombotic events

Stotts et al. Semin Liv Dis 2021

PVT in Cirrhosis: Initial diagnosis

- Presentation ranges from asymptomatic (incidentally found) to severe portal hypertension-related complications or intestinal ischemia
- No guidelines to suggest screening asymptomatic patients
    - Typically assessed q6mo via US for HCC screening
    - Some advocate for q3mo US for waitlisted patients
- Imaging modality
    - Doppler US as first-line (sensitivity and specificity 80-100%)
        - Caveats: bowel gas, obesity, thrombus characteristics (incompletely occlusive, PV trunk posterior to duodenum, SMV involvement)





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PVT in Cirrhosis: Defining the thrombus

Malignant features

Modality	Characteristics	Sensitivity	Specificity
CT	PVT diam > 23cm *OR* neovascularity	86%	100%
MRI	2/3: distance from tumor to PVT <2cm, tumor size >5cm, arterially-enhancing thrombus	100%	90%
A-VENA (CT or MRI)	3+ of: AFP > 1000 ng/dL, venous expansion, arterially-enhancing thrombus, neovascularity, proximity to HCC	100%	94%

- Confirm thrombus and define extent with contrasted cross-sectional imaging
  - CT vs. MRI: local availability / expertise and patient factors
  - EUS with lower sensitivity (81%) and specificity (93%), cannot definitively assess for HCC or mesenteric infarction
- Determine acuity
  - Recent: hypoechogenic (US) or hypodense (CT)
  - Chronic: fibrosis of MPV, collateralization, cavernous transformation, calcification (pathognomonic)
    - Some literature suggests cavernoma forms within 6-20 days
- Rule out malignancy (12-20% of HCC associated with PVT)

Stotts et al. Semin Liv Dis 2021

PVT in Cirrhosis: Describing the thrombus

*NOTE: Lots of classification systems exist but lack clinical utility outside of LT / short-term outcomes

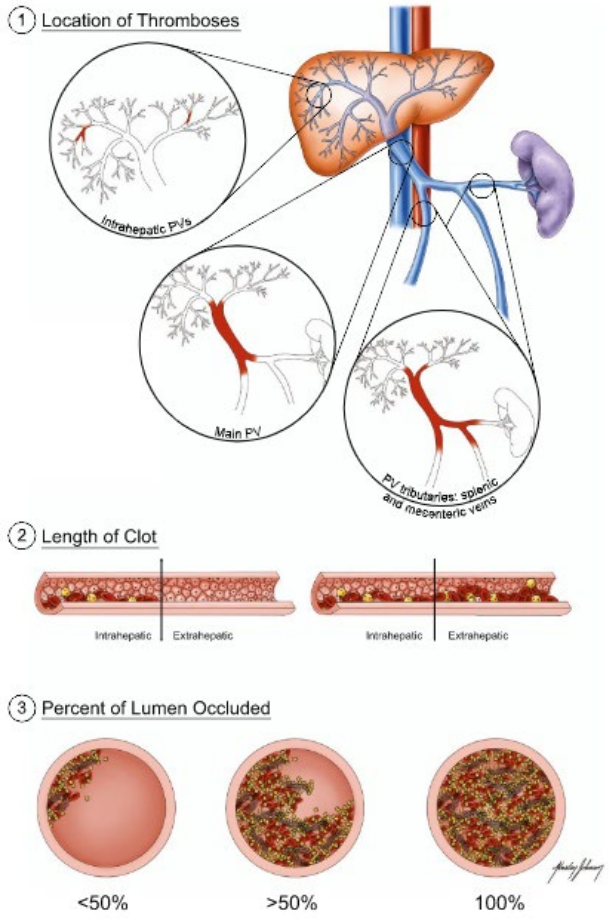


FIG. 3. The important components of PVT in clinical practice and research design.

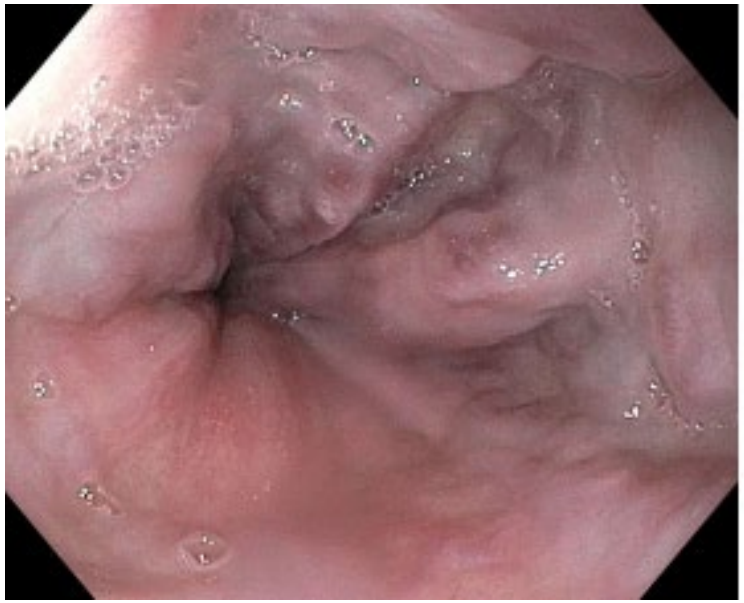
TABLE 5. Recommended Standardized Nomenclature for Description of PVT in Both the Clinical and Research Setting

Descriptor	Definition
Time course	
Recent	PVT presumed to be present for <6 months
Chronic	PVT present or persistent for >6 months
Percent occlusion of main PV	
Completely occlusive	No persistent lumen
Partially occlusive	Clot obstructing >50% of original vessel lumen
Minimally occlusive	Clot obstructing <50% of original vessel lumen
Cavernous transformation	Gross portoportal collaterals without original PV seen
Response to treatment or interval change	
Progressive	Thrombus increases in size or progresses to more complete occlusion
Stable	No appreciable change in size or occlusion
Regressive	Thrombus decreases in size or degree of occlusion

Northup et al. Hepatology 2021

PVT in Cirrhosis: Management

- EGD to assess for gastroesophageal varices
    - Management per societal guidelines
- Evaluate patient-specific factors
    - Functional status / mobility
    - Active alcohol use
    - Reliability of follow-up / medication adherence
    - History of bleeding
    - Current symptom burden, chronicity
    - Transplant eligibility
- 3 treatment strategies
    - “Wait-and-See”
    - Systemic anticoagulation
    - TIPS placement



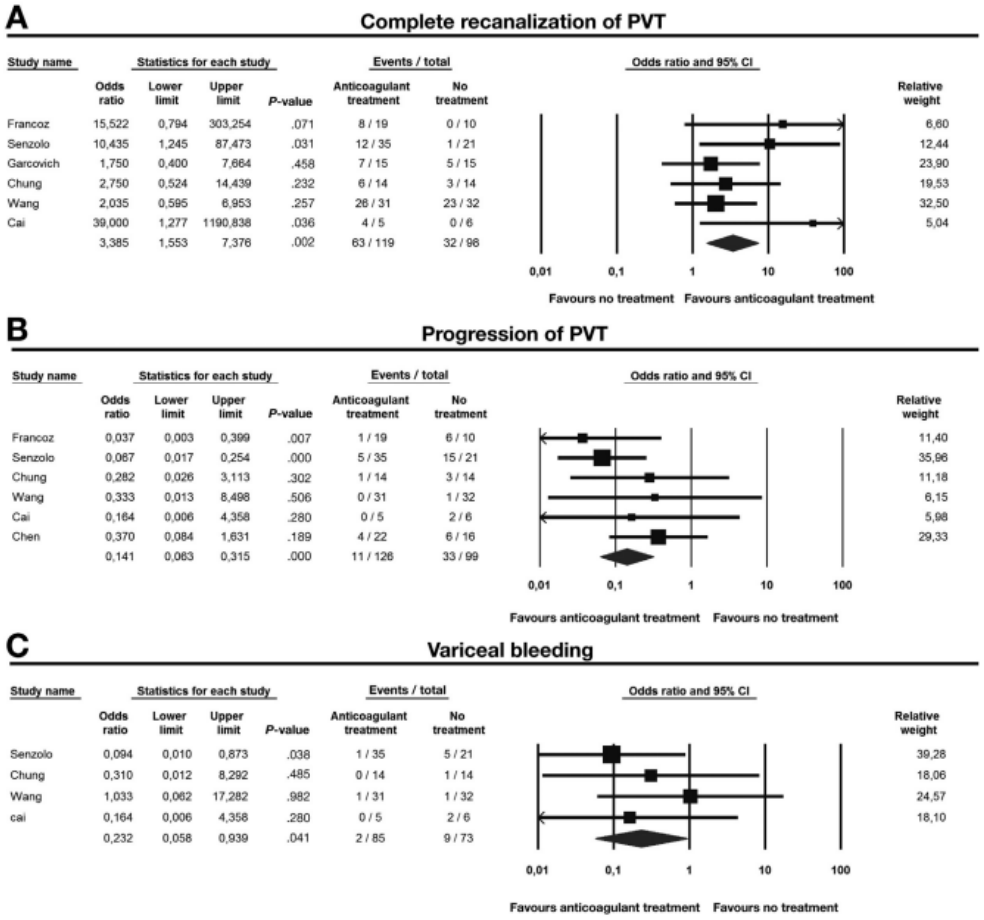
Stotts et al. Semin Liv Dis 2021

PVT in Cirrhosis: "Wait-and-See"

- 40% of PVTs will spontaneously re-canalize
- Reasonable to consider if strong contraindications to anticoagulation and/or asymptomatic and not transplant candidate
- Re-evaluate for new symptoms and repeat imaging in 3-6 weeks to assess for progression and/or spontaneous recanalization → initiate systemic anticoagulation if worsening

Stotts et al. Sem Liver Dis 2021

PVT in Cirrhosis: Systemic anticoagulation

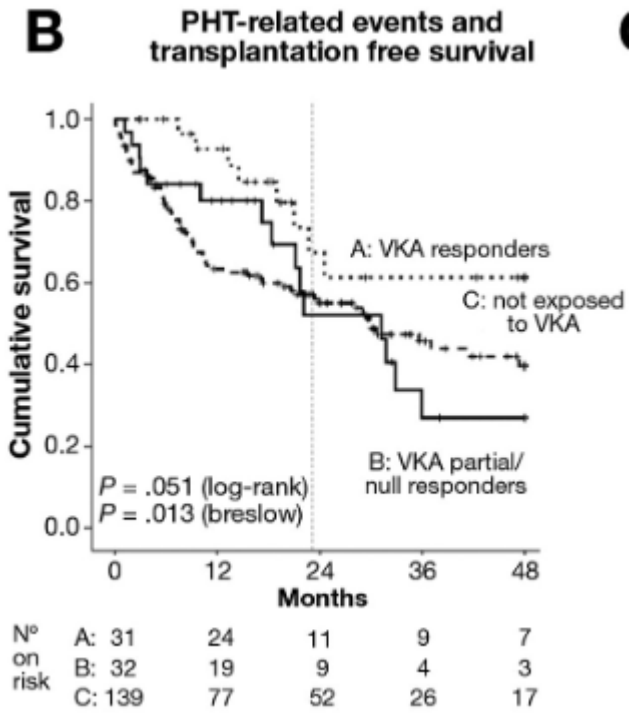


- Improved complete + partial recanalization rates vs. no anticoagulation (71% vs. 42%)
- Reduction in PVT progression vs. no anticoagulation (9% vs. 33%)
- No difference in overall bleeding rates vs. no anticoagulation
- Decreased variceal bleeding rate vs. no anticoagulation (2% vs. 12%)

Loffredo et al. Gastroenterology 2017

PVT in Cirrhosis: Systemic anticoagulation

- Potential benefit even in patients with compensated cirrhosis *if complete recanalization*
- Felt to offset increase in minor bleeding events – more portal HTN related rather than effect of the anticoagulant



La Mura et al. Clin Gastroenterol Hepatol 2018

PVT in Cirrhosis: Systemic anticoagulation

Table 2. Predictors of Radiologic Response to Anticoagulation Therapy

	Complete or partial response (n = 33)	No response (n = 22)	*P* value
Age (*y*)	56.6 ± 12.8	58.6 ± 9.8	.538
Gender (male) (%)	82	77	.739
Previous PH bleeding, yes/no	13/20	11/11	.580
Previous ascites, yes/no	21/12	14/8	1.000
Previous HE, yes/no	4/29	3/19	1.000
Any previous PH decompensation, yes/no	27/6	17/5	.739
Child–Pugh score at diagnosis	7.4 ± 2.1	7 ± 1.7	.389
Platelet count ($\times 10^9$/L)	125 ± 110	95 ± 92	.295
Creatinine (*mg/dL*)	0.9 ± 0.27	0.9 ± 0.24	.990
Presence of underlying thrombophilia (%)	16	22	.701
Presence of symptoms at diagnosis (%)	42	23	.158
Involvement of SV (%)	33	18	.354
Involvement of SMV (%)	40	56	.375
Involvement of entire venous axis with independence of its grade (%)	24	18	.744
More than 1 vessel affected (%)	55	41	.412
Presence of ascites at diagnosis of PVT (%)	75	70	.574
Indication of anticoagulation: (%) recent/progression	58/42	55/45	1.000
Delay in initiation of anticoagulation (*d*)	15 ± 27	55 ± 86	.042
Start of anticoagulation			.044
≤14 days	25	10	
>14 days	8	12	
Duration of anticoagulation (*mo*)			.249
<6	13	5	
>6	20	17	
Duration of anticoagulation (*mo*)			.674
<3	3	3	
>3	30	19	

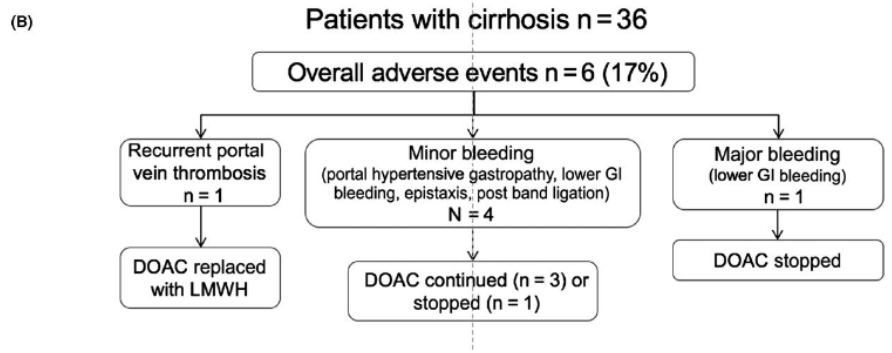
HE, hepatic encephalopathy; PH, portal hypertension.

- Optimal timing of initiation
  - If severe symptoms or mesenteric ischemia, immediate
  - Otherwise, unsettled
    - Within 14d vs. up to 6 months

Delgado et al. Clin Gastroenterol Hepatol 2012

PVT in Cirrhosis: Systemic anticoagulation

- Choice of agent
  - Historical: UFH, LMWH, VKA → both 'bridge' and monotherapy have demonstrated recanalization benefit
    - Problems with monitoring therapy: INR, anti-Xa levels inaccurate
  - DOACs: increasing in popularity
    - Patients w/ cirrhosis excluded from clinical trials
    - Accepted use in Child-Pugh A and B patients; significant caution in Child-Pugh C
    - Reversal agents available



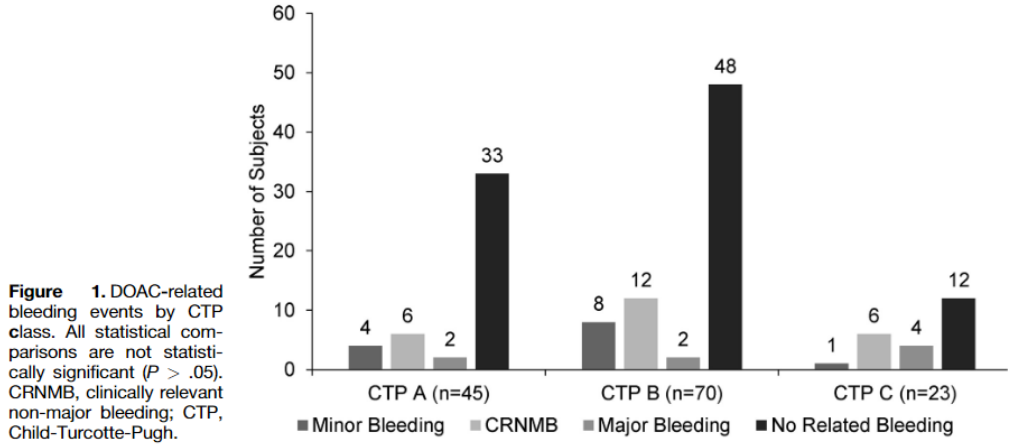


Figure 1. DOAC-related bleeding events by CTP class. All statistical comparisons are not statistically significant ($P > .05$). CRNMB, clinically relevant non-major bleeding; CTP, Child-Turcotte-Pugh.

De Gottardi et al. Liv Int 2017; Mort et al. Clin Gastroenterol Hepatol 2020

PVT in Cirrhosis: Systemic anticoagulation

- Optimal duration of therapy – ***unsettled***
    - Serial imaging: 2-3 months after initiation, then q6mo
    - Anticoagulation: at least 6 months if non-waitlisted; indefinitely until transplant if waitlisted (stop post-transplant)

- Choice of agent in patients near transplant – based on provider comfort, availability of reversal agents

PVT in Cirrhosis: TIPS

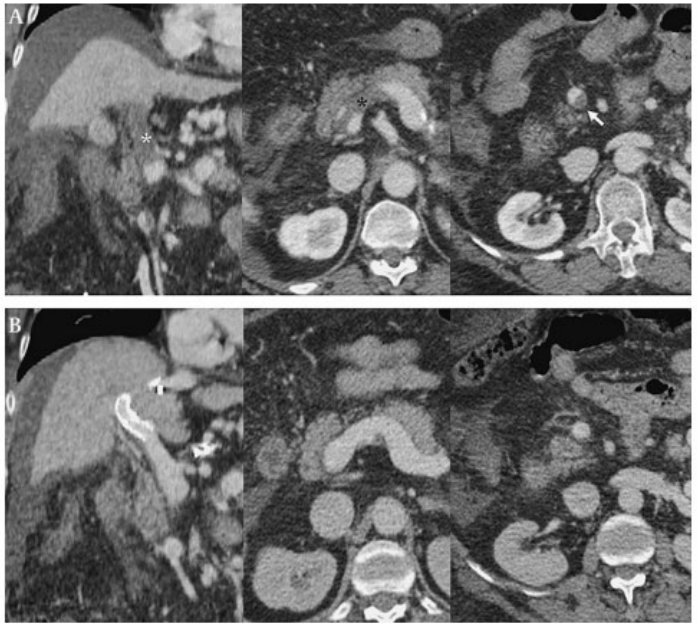


Figure 2 (A) MDCT shows severe and extensive PVT with lumen occupancy of the MPV of 100% (white star), SMV 50% (white arrow) and splenic vein 100% (black star). (B) 36 days after TIPS placement, MDCT shows complete recanalisation. MDCT, multidetector computed tomography; MPV, main portal vein; PVT, portal vein thrombosis; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepatic portosystemic shunt.

- Classically, PVT was a contraindication
- Paradigm shift – added benefit of managing portal hypertensive complications
- Risk of HE similar to TIPS placement for other indications
- In highly specialized centers, trans-splenic or trans-hepatic approaches for recanalization and TIPS placement (TIPS-PVR) report excellent technical success and patency for chronic PVT

Luca et al. Gut 2011

PVT in Cirrhosis: Prophylaxis?

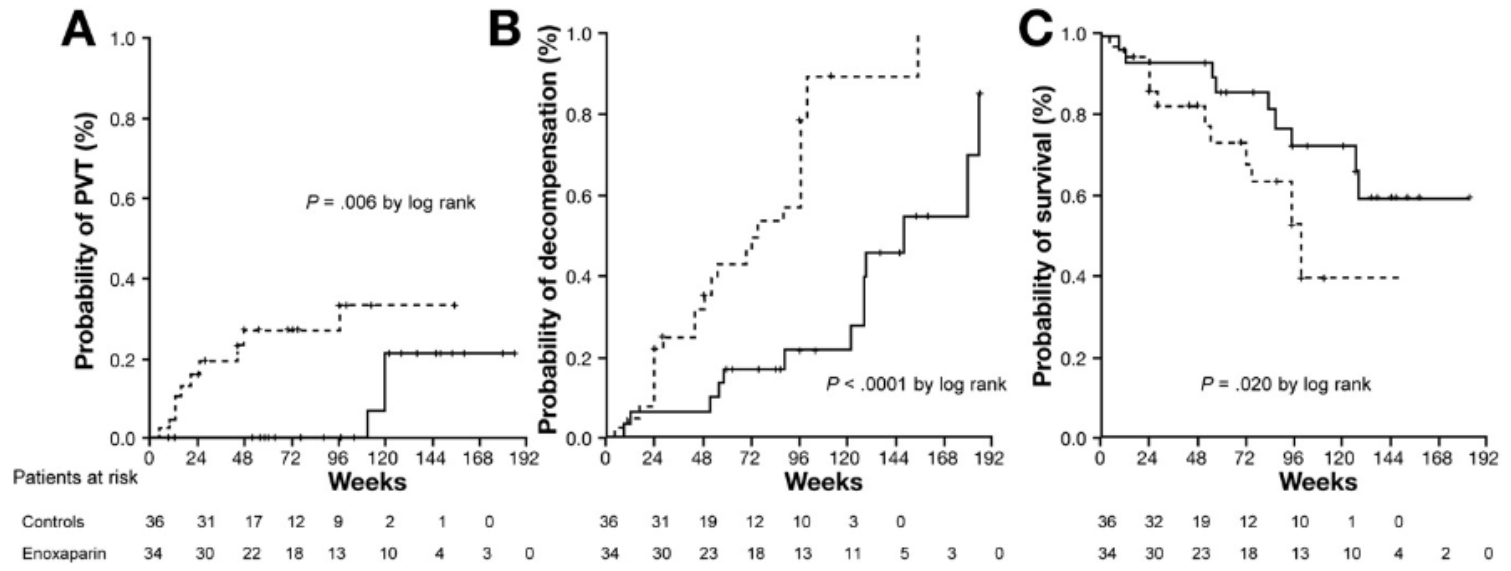


Figure 1. Actuarial probability of developing PVT or hepatic decompensation, and probability of survival according to treatment group. Probability of remaining free from (*A*) PVT, (*B*) hepatic decompensation, and (*C*) probability of survival. *Dashed line*: controls; *continuous line*: enoxaparin-treated patients.

70 patients (Child-Pugh B7-C10),
prophylactic dose enoxaparin for 48 weeks (n = 34) vs. control (n = 36)

Villa et al. Gastro 2012

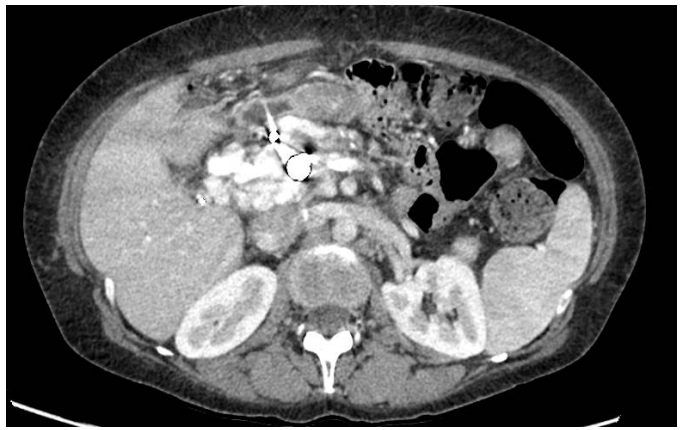
PVT in the non-cirrhotic patient

- Autopsy suggests prevalence of 0.05%
- Often, but not always, associated with an underlying thrombophilia
    - Workup, guided by a hematologist, typically recommended if lack of clear provoking factor
- More urgency to initiate anticoagulation to avoid clot propagation and progression to AMI and portal hypertension
    - DOAC use becoming more common
- EGD to assess for varices
- TIPS-PVR has also been described in this population
- Large cohort study of 330 patients followed for mean 41.6 months receiving DOAC (93) vs. warfarin (108) vs. LMWH (70) vs fondaparinux (2) vs. no anticoagulation (57)
    - ***DOACs with superior complete radiographic resolution, recanalization rate, and bleeding rates vs. warfarin***

Condition
Inherited or acquired thombophilic disorder (G20210A prothrombin gene mutation most common)
Myeloproliferative neoplasm (JAK2 mutation most common)
Surgery
IBD
Pancreatitis
Appendicitis
Diverticulitis
Omphalitis (umbilical vein catheterization in infants)

Naymagon et al. Blood Adv 2020

Portal Biliopathy



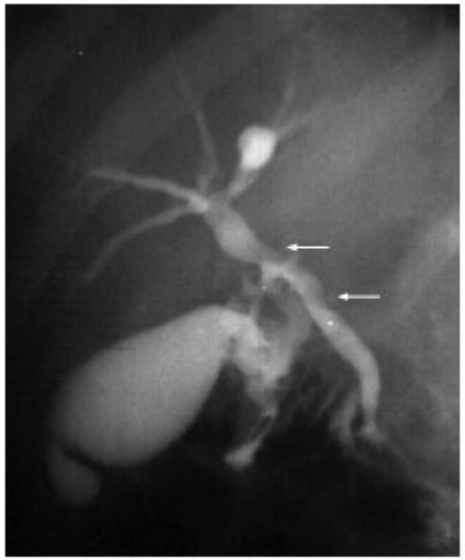


Figure 2 Endoscopic retrograde cholangiogram in a patient with extrahepatic portal venous obstruction showing irregular intrahepatic ducts and indentations of common hepatic and bile duct (arrows) arising due to compression by veins of the portal cavernoma.

- Long-term sequela of portal cavernoma
- Chronic PV occlusion → enlargement of biliary plexuses (epicholedochal venous plexuses of Saint and Petren) → compression of extrahepatic biliary tree
- Symptoms: abdominal pain, jaundice, cholangitis, choledocholithiasis, biliary strictures
- Management: ERCP for sphincterotomy, lithotripsy, biliary stent placement; surgical bilioenteric anastomosis

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Hepatic Vein Thrombosis (Budd-Chiari)

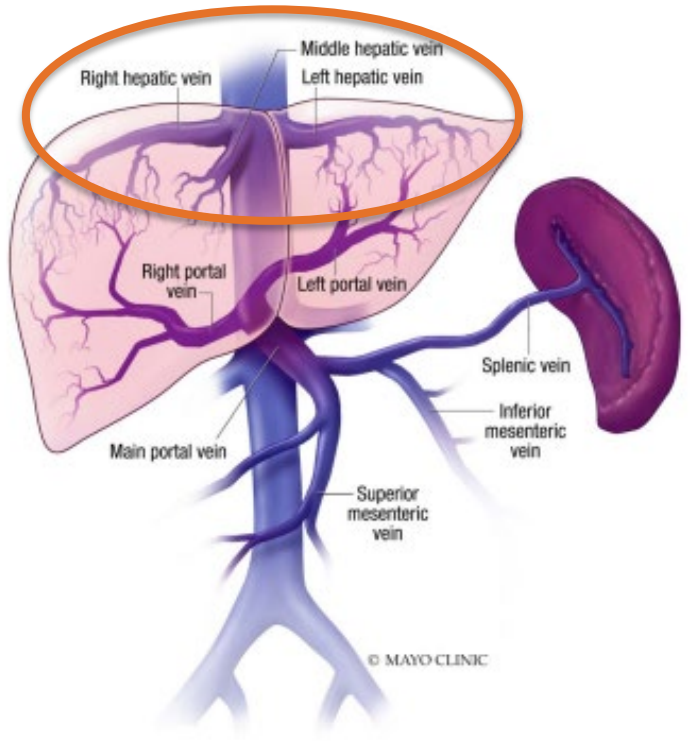


Figure 1. Hepatic and portal venous system.

Hepatic Vein Thrombosis (Budd-Chiari)

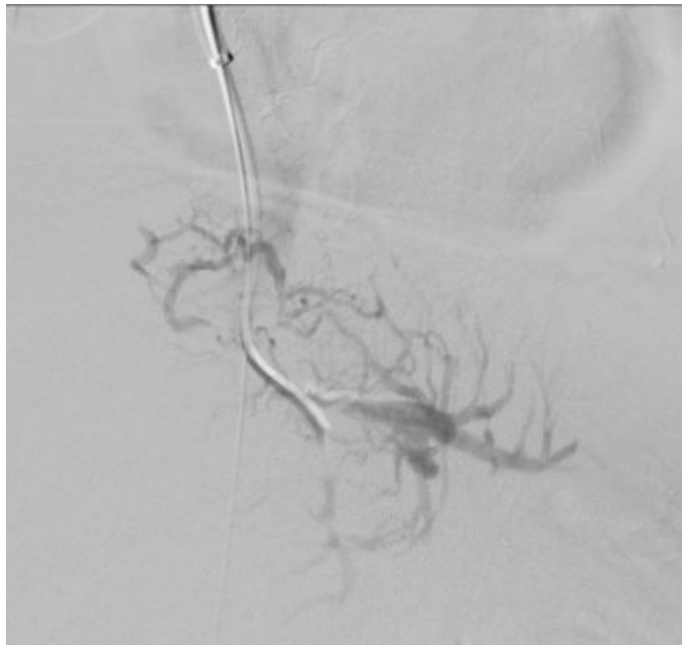
- Rare disorder, incidence < 1 per million person-years (prevalence 1.4—7.69 per million person-years
- Associated with hypercoaguable state in 75% of patients
    - Workup recommended in most patient, directed by hematology
- Presentation varies – asymptomatic to ALF (depends on extent of obstruction)
    - Triad of abdominal pain, hepatomegaly, and ascites classic
- Formation of esophageal varices
- 40% develop nodular liver lesions
    - NRH >> adenomas, HCC (requires biopsy to diagnose – cannot use LIRADS)
    - Q6mo US +/- AFP screening

TABLE 8. Recommendations and Limitations of Specialty Testing for Thrombophilic Conditions

Specialty Test*	Cohort to Be Tested	Limitations
JAK2 V617F mutation[328]	PVT/HVT in the absence of major provoking factor†	• Occult MPN is frequent; this test should be performed, even if CBC is not suggestive. • If negative in the presence of thrombocytosis or clinical concern for polycythemia vera, further tests are needed to exclude an MPN.
CALR mutation[327]	PVT/BCS in the absence of major provoking factor if JAK2 negative†	• Significant positive predictive value with platelet count >200,000/μL together with splenomegaly >15 cm in the context of severe portal hypertension
Antiphospholipid antibodies[345,346] • Cardiolipin antibodies • Beta2 glycoprotein antibodies • Lupus anticoagulant	PVT/BCS in the absence of major provoking factor†	• Solid-phase IgG and IgM anti-beta-2 glycoprotein-1 and anticardiolipin antibodies can be tested in the acute phase. • Antibodies of potential clinical significance if >40 GPL units or MPL units or >99th percentile • Diagnosis of antiphospholipid syndrome requires persistence of antibodies on repeat testing ≥12 weeks. • Lupus anticoagulant should not be tested in the acute phase because acute changes and anticoagulation can interfere.
Paroxysmal nocturnal hemoglobinuria flow cytometry[330]	PVT/BCS in the absence of major provoking factor†	• Increased index of suspicion if current/preexisting hemolytic anemia and/or cytopenias • Extremely rare disease
Heritable thrombophilia • Factor V Leiden • Prothrombin gene polymorphism • Protein C deficiency • Protein S deficiency • Antithrombin deficiency	Not routinely recommended	• Results do not generally influence management. • Proteins C, S, and antithrombin can be low in the context of acute thrombosis and/or liver disease and may not reflect an inherited deficiency.

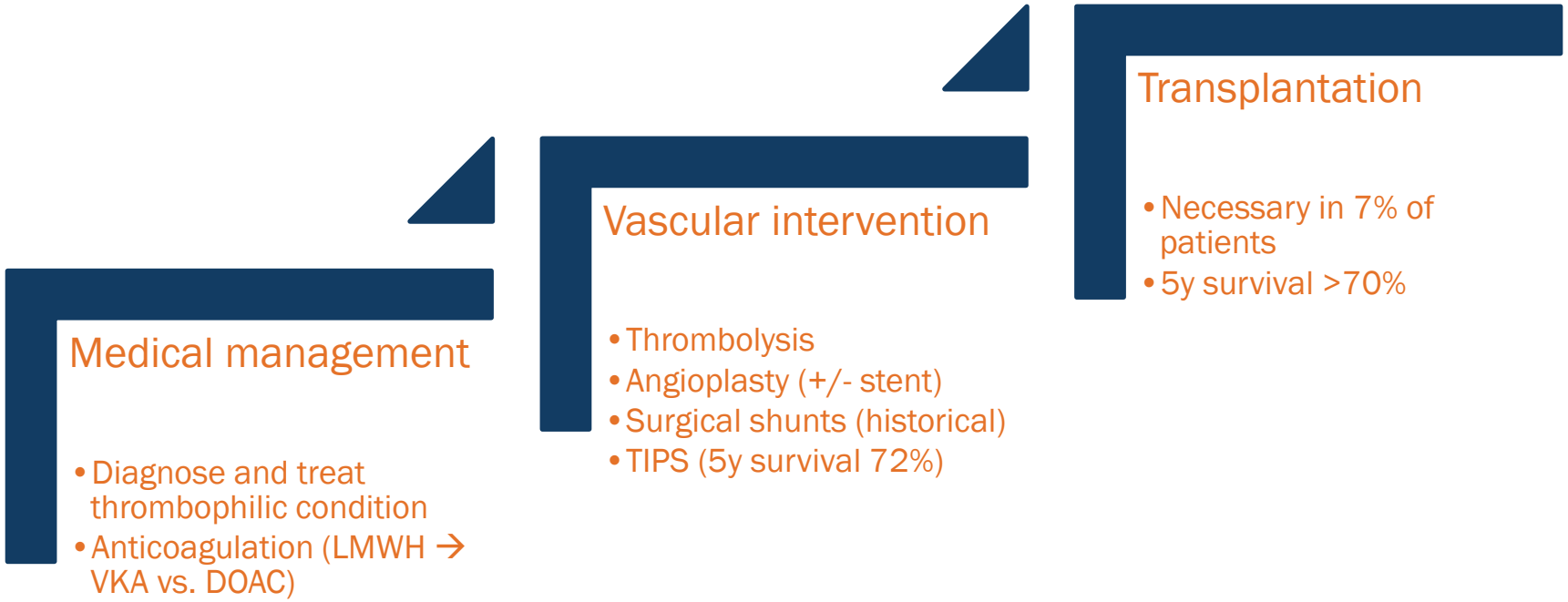
Northup et al. Hepatology 2021

Hepatic Vein Thrombosis (Budd-Chiari)



- Doppler ultrasound with sensitivity >75%
- Can confirm with CT or MRI
- Hepatic venography may be necessary if high suspicion and other modalities non-diagnostic; helps detect webs (vs. thrombus)
- Need to identify if hypercoaguable state exists and treat
- Management done in graded fashion

Hepatic Vein Thrombosis (Budd-Chiari)



Idiopathic non-cirrhotic portal HTN

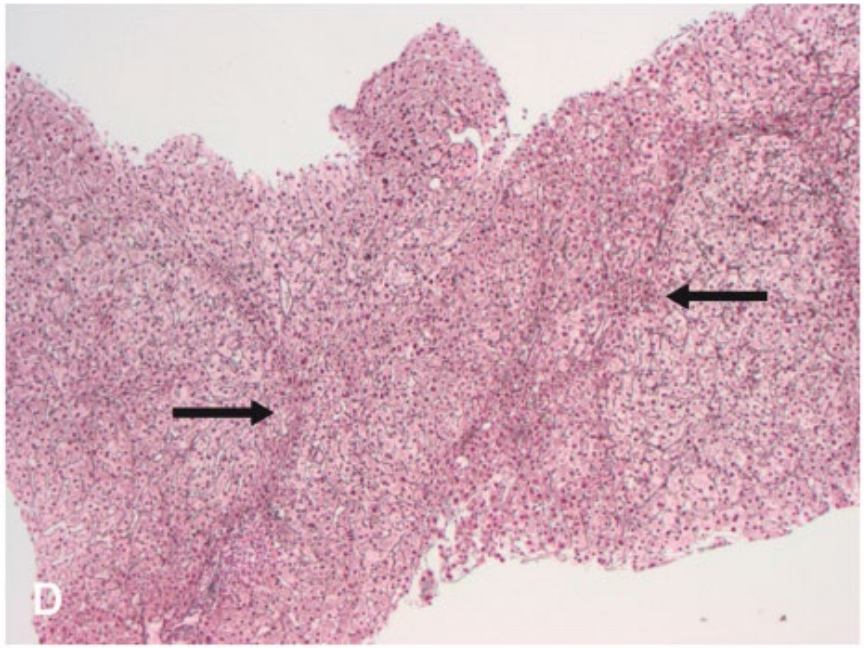
- Portal HTN in absence of cirrhosis, PV obstruction, HVT/BCS, sarcoidosis, congenital hepatic fibrosis, and schistosomiasis
    - Caused by portosinusoidal vascular disease (PSVD)
- Pathophysiology:
    - Microvascular injury to small intrahepatic portal vein branches → obliteration leading to "obliterative portal venopathy" → irregular distribution of blood flow → atrophic areas and regenerative areas → nodular regenerative hyperplasia → incomplete septal fibrosis

TABLE 2 Conditions That Have Been Associated With INCPH

Type	Specific Condition	Purported Mechanism
Autoimmune	Autoimmune hepatitis Primary biliary cirrhosis Systemic lupus erythematosus Scleroderma Rheumatoid arthritis Common variable immune deficiency Celiac disease	Immune-mediated venulitis and/or thrombophilia leading to obliteration and then fibrosis
Infectious	Repeated gastrointestinal infections HIV	Septic emboli to portal venules Hypercoagulability, didanosine
Drug-induced	Didanosine Azathioprine 6-Thioguanine Oxaliplatin	Toxic injury
Prothrombotic	Myeloproliferative disorder Protein C/S deficiency Factor II deficiency ADAMTS13 deficiency	Chronic microthrombi in portal venules leading to fibrosis and obliteration
Genetic	Turner's syndrome Adams-Oliver syndrome Familial cases	Abnormal development or vascular malformations Confers susceptibility in face of other conditions?

Garcia-Tsao et al. Clin Liv Dis 2015

Idiopathic non-cirrhotic portal HTN



Nodular regenerative hyperplasia

- Spectrum:
  - Initially, pre-sinusoidal portal HTN, then progresses to mimic cirrhosis over time
  - Wide-range of clinical features – variceal bleeding most common
    - Ascites and HE often in context of bleeding and typically can be medically managed
- Minimal to no elevation of liver stiffness or HVPG
- Liver biopsy required to r/o cirrhosis and identify specific lesions
  - Reticulin staining helpful to assess architecture
- FNH-like lesions seen in 14%, adenomas and HCC rare
- PVT risk higher than in cirrhosis (32% vs. 18%)
- Portal HTN management, LT for typical indications

Schouten et al. OJRD 2015

Sinusoidal obstruction syndrome (SOS)

- Also known as veno-oclusive disease (VOD)
- Seen in up to 15% of adults after hematopoietic stem cell transplant
- Risk factors:
    - Pre-existing liver disease (particularly cirrhosis): 3-10x increased risk
    - Reduced lung diffusion capacity
    - Increased age
    - Underlying leukemia
    - Myeloablative conditioning with alkylating agents (busulfan, cytarabine, cyclophosphamide): 2-8x increased risk
    - Allogenic (vs. autologous) graft
    - GVHD prophylaxis with sirolimus (+cyclophosphamide/total body irradiation) and methotrexate (busulfan or etoposide)

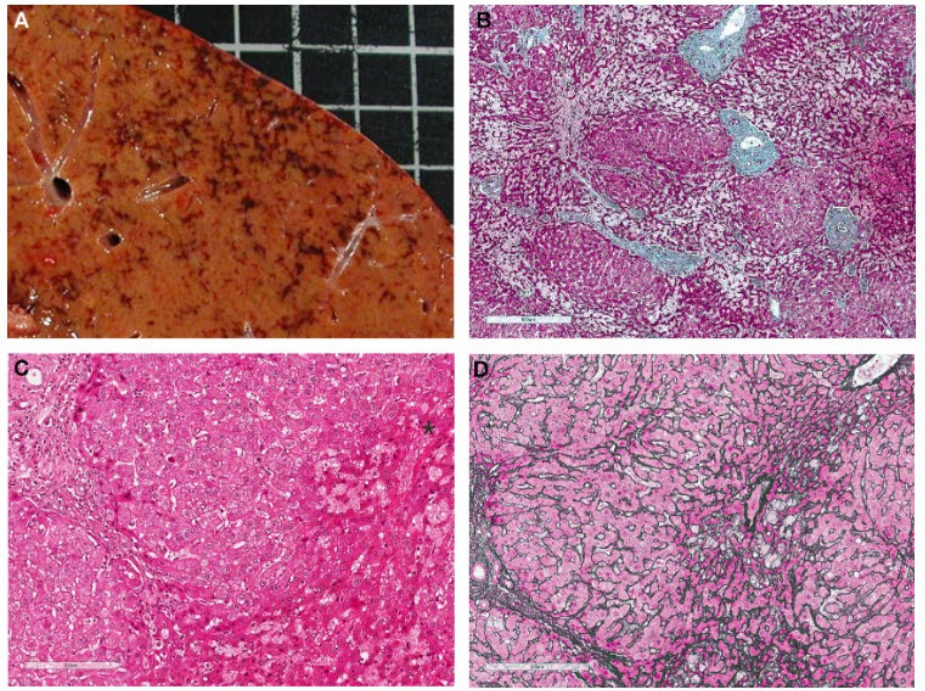


Figure 1 Sinusoidal obstruction syndrome related to oxaliplatin use for colo-rectal metastatic liver disease (A: fresh cut section of hepatectomy for metastasis, B: Masson trichrome, C: hematein eosin-safran, D: argentation stain): Grossly, diffuse liver congestion has a typical nutmeg aspect corresponding on histology to extensive veno-venous dilatation and congestion around small hepatic veins*; centrilobular hepatocytes plates are atrophic or disrupted and a sinusoidal fibrosis is frequently observed without venous obliteration.

Valla and Cazalas-Hatem. Clin Res Hepatol Gastroenterol 2016.

Sinusoidal obstruction syndrome (SOS)

- Also seen with use of oxaliplatin, pyrrolizidine alkaloid use (bush tea), high-dose liver radiation, Y-90 for liver tumors, liver transplantation
- Pathogenesis: cellular injury by toxic metabolites → damage to sinusoidal endothelium → cellular debris passes into space of Disse and narrows venous lumen to create sinusoidal venous outflow obstruction → post-sinusoidal portal HTN
- Symptoms: weight gain, edema, hepatomegaly, ascites, jaundice
- Signs: thrombocytopenia (refractory to transfusion), elevated liver enzymes, increased PT/INR
- Ultrasound can assist but not make diagnosis
- Liver biopsy can be helpful

Valla and Cazalas-Hatem. Clin Res Hepatol Gastroenterol 2016.

SOS: Diagnosis

Table 1 Two widely used sets of criteria for a clinical diagnosis of veno-occlusive disease.

Seattle criteria	Baltimore criteria
Within 20 days of transplantation, two of three findings among the following	*Within 30 days of transplantation, bilirubinemia > 34.2 mol/L (2 mg/dL), plus 2 other findings among the following*
Bilirubin > 34.2 mol/L (2 mg/dL)	Hepatomegaly, usually painful
Hepatomegaly or RUQ pain of liver origin	> 5% weight gain
> 2% weight gain due to fluid accumulation	Ascites

Table 1 EBMT criteria for SOS/VOD diagnosis in adults

Classical SOS/VOD	Late-onset SOS/VOD
In the first 21 days after HSCT	>21 days after HSCT
Bilirubin ≥ 2 mg/dL and two of the following criteria must be present: - Painful hepatomegaly - Weight gain > 5% - Ascites	Classical VOD/SOS beyond day 21 OR Histologically proven SOS/VOD OR Two or more of the following criteria must be present: - Bilirubin ≥ 2 mg/dL (or 34 µmol/L) - Painful hepatomegaly - Weight gain > 5% - Ascites AND hemodynamical or/and ultrasound evidence of SOS/VOD

These symptoms/signs should not be attributable to others causes

Valla and Cazalas-Hatem. Clin Res Hepatol Gastroenterol 2016. Mohty M et al. Bone Marrow Transplant 2016.

SOS: Diagnosis

Table 3. New EBMT criteria for severity grading of a suspected SOS/VOD in adults

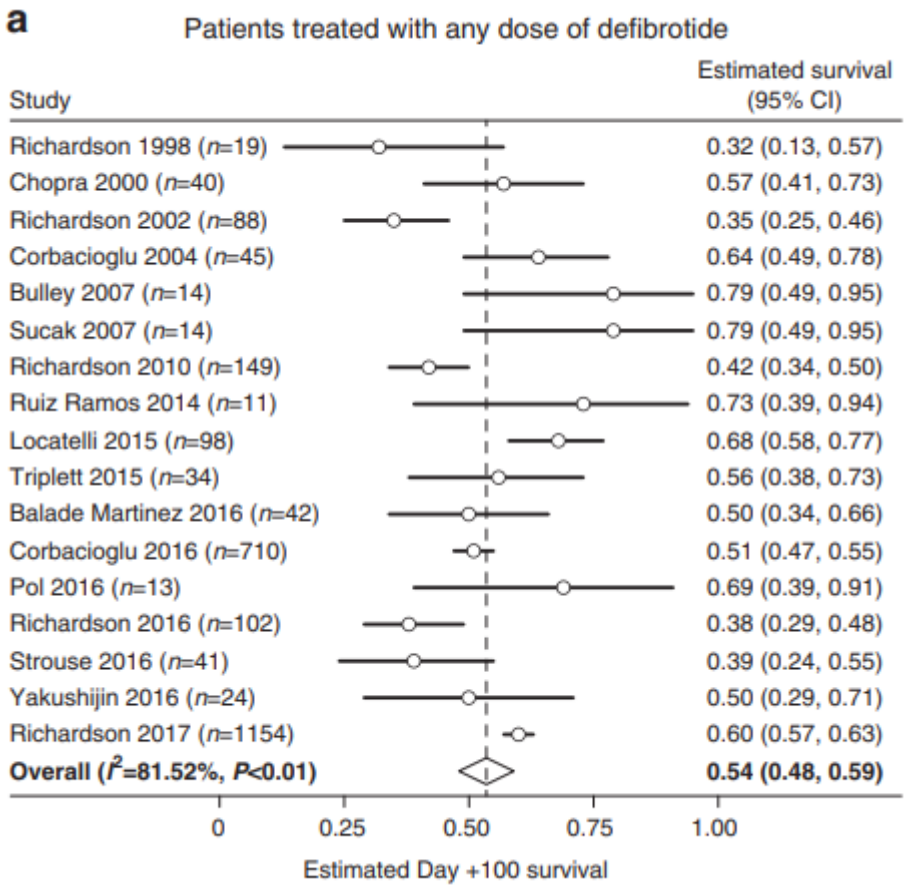
	Mild[a]	*Moderate*[a]	*Severe*	*Very severe - MOD/MOF*[b]
Time since first clinical symptoms of SOS/VOD[c]	>7 Days	5–7 Days	⩽4 Days	Any time
Bilirubin (mg/dL) Bilirubin (μmol/L)	⩾2 and <3 ⩾34 and <51	⩾3 and <5 ⩾51 and <85	⩾5 and <8 ⩾85 and <136	⩾8 ⩾136
Bilirubin kinetics			Doubling within 48 h	
Transaminases	⩽2 × normal	> 2 and ⩽5 × normal	>5 and ⩽8 × normal	>8 × Normal
Weight increase	< 5%	⩾5% and <10%	⩾5% and <10%	⩾10%
Renal function	<1.2 × baseline at transplant	⩾1.2 and <1.5 × baseline at transplant	⩾1.5 and <2 × baseline at transplant	⩾2 × baseline at transplant or others signs of MOD/MOF

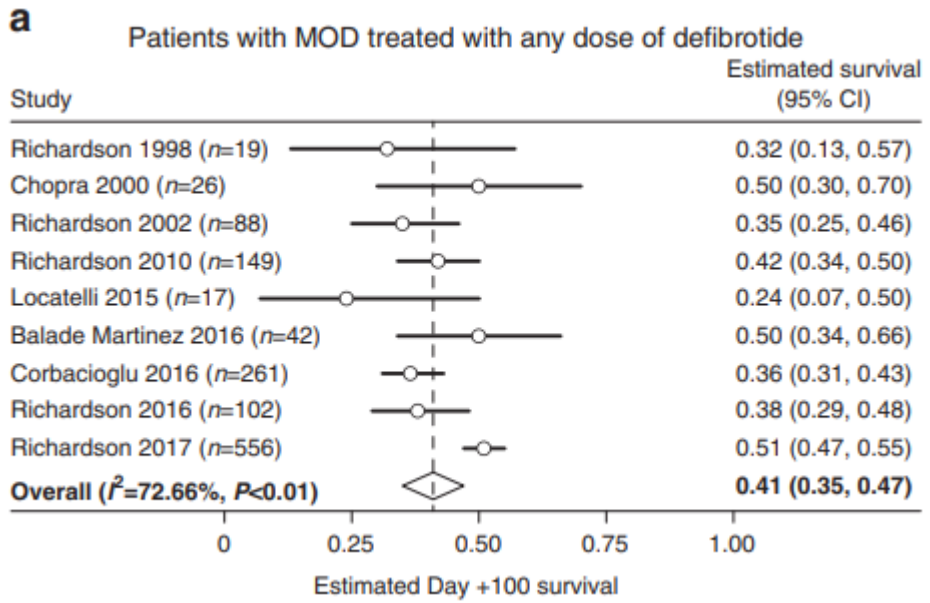
Valla and Cazalas-Hatem. Clin Res Hepatol Gastroenterol 2016. Mohty M et al. Bone Marrow Transplant 2016.

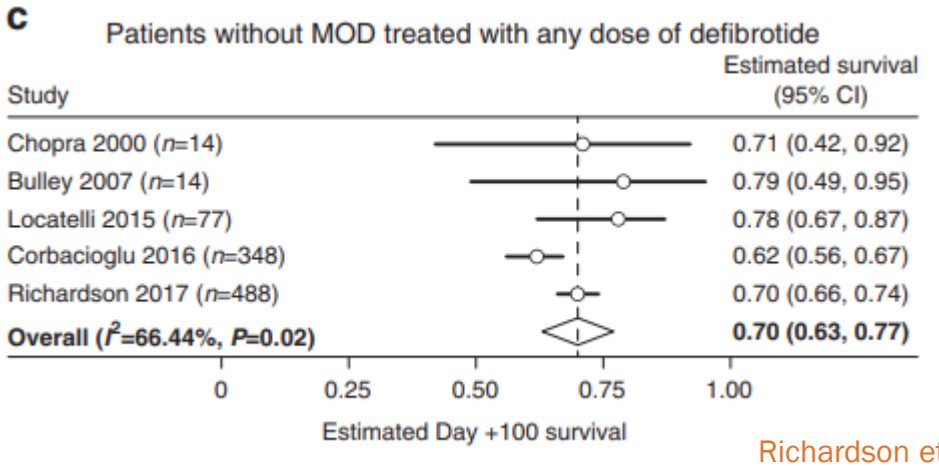
SOS: Diagnosis & Management

- Differential diagnosis: engraftment syndrome, acute graft-versus-host-disease, hepatic infections, drug toxicity, Budd-Chiari
- Prophylaxis: **UDCA**
    - Cochrane review of 4 trials reduced incidence of SOS by 40% and decreased mortality from SOS by 73% but no difference in overall survival
- Treatment by severity
    - Mild/moderate: supportive care
    - Severe: **defibrotide** (single-stranded oligodeoxyribonuclotides from DNA of porcine intestinal mucosa), may help with endothelial protection, restore thrombo-fibrinolytic balance, have anti-inflammatory properties
        - 6.25mg/kg every 6h IV for at least 21 days up to 60 days
        - Early initiation and duration >3 weeks improves overall survival

Valla and Cazalas-Hatem. Clin Res Hepatol Gastroenterol 2016. Mohty M et al. Bone Marrow Transplant 2016.



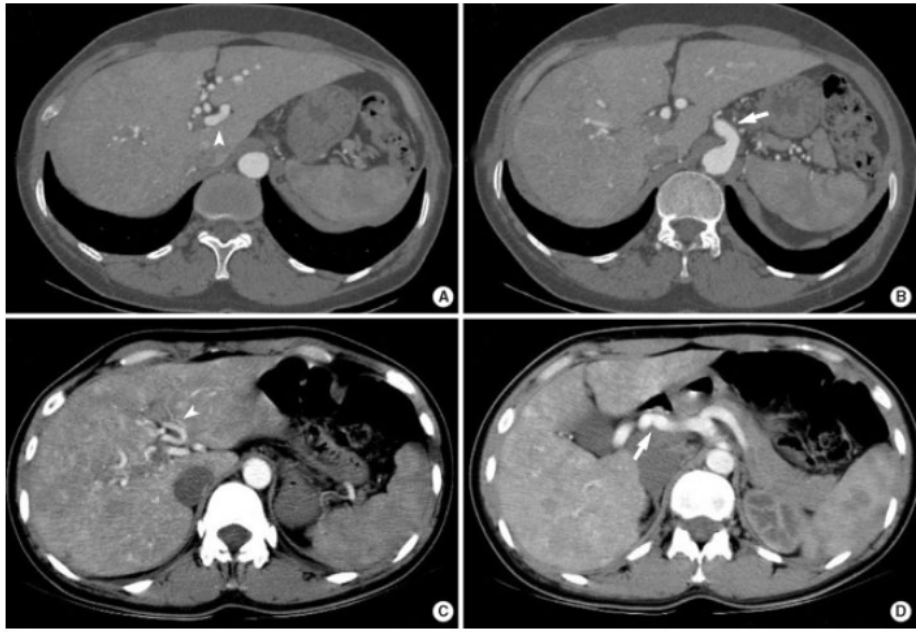




Richardson et al. BMT 2019

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu)

- Rare, autosomal dominant genetic disease
- Diffuse AVMs involving skin, mucous membranes, lungs, brain, GIT, and liver
- **Liver vascular malformations (LVMs)** in 40-70%, increases mortality
    - 3 types:
        - Hepatic artery to hepatic vein (most common)
        - Hepatic artery to portal vein
        - Portal vein to hepatic vein
- Often detectable in setting of liver bruit and cross-sectional imaging findings
    - Heterogenous liver enhancement, hypervascular liver, common hepatic artery enlargement



Radiology findings of the HHT patients. (A) and (B) CT angiography of the liver in patient 1 shows an enlarged celiac axis (arrow), a prominent hepatic artery (arrowhead) with multiple aberrant collateral vessels, and heterogeneous attenuation of the liver. (C) and (D) Abdominal CT of patient 3 shows severe tortuous dilatation of the hepatic artery (arrow) and its intrahepatic branches (arrowhead) with mottled hepatic enhancement.

Lee ST et al. J Korean Med Sci 2009; Simonetto DA et al. Am J Gastroenterol 2020.

Complications of LVMs

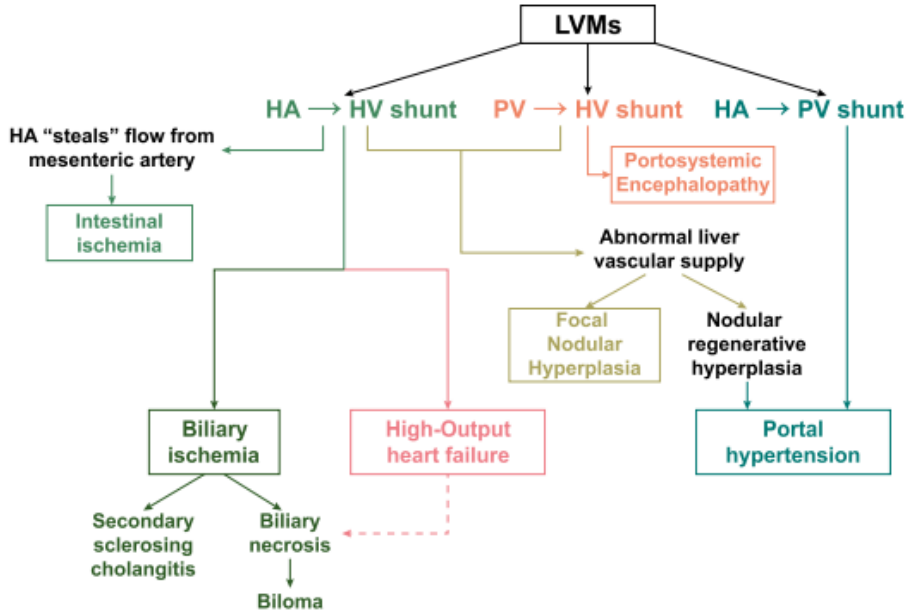


FIG. 5. Pathophysiology of the various clinical presentations of HHT.

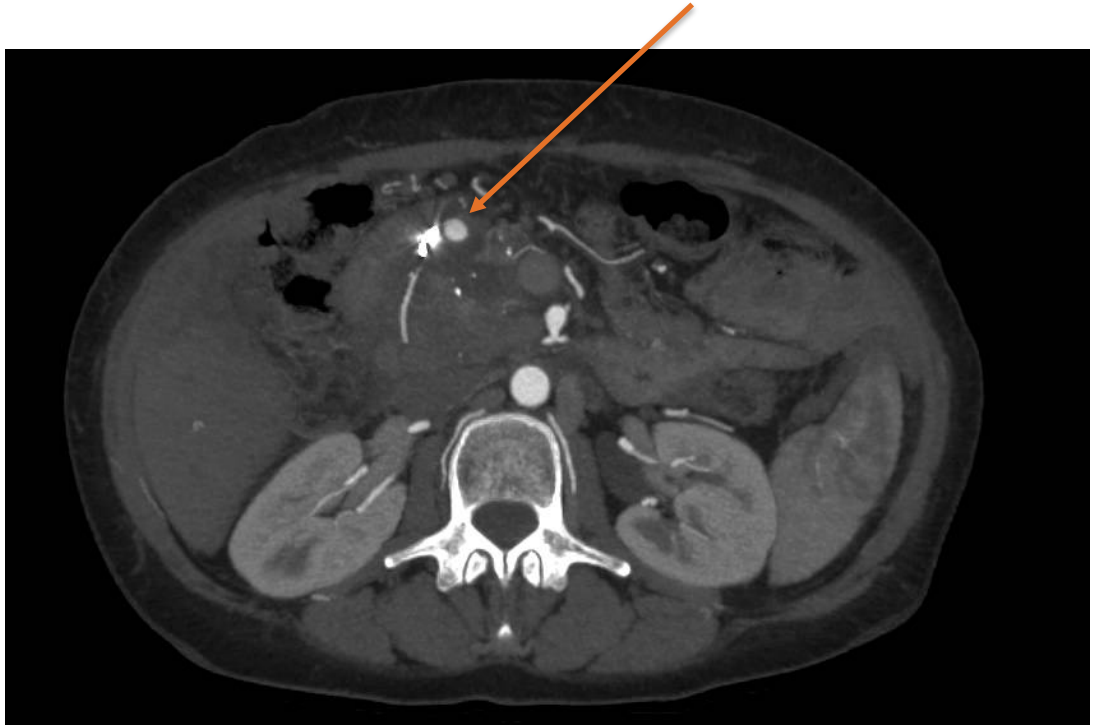
Northup PG et al. Hepatology 2021.

Management of HHT and LVMs

- If asymptomatic, no therapy
- Symptomatic – manage at tertiary care center to treat sequelae of heart failure, anemia, biliary complications, portal HTN
    - Adequate in >60% of patients
    - Non-responders – bevacizumab to inhibit VEGF, liver transplantation (↑ complications)
        - Hepatic artery embolization / surgical ligation may induce long-term harm – hepatobiliary necrosis
- LVMs can recur as early as 6y post-LT

Hepatic artery aneurysm

- Rare – incidence of 0.1-0.2%
- True aneurysm (all 3 arterial wall layers) vs. pseudoaneurysm (localized wall disruption and contained blood by perivascular tissue)
- Aneursymal etiologies:
    - Atherosclerosis, mediointimal degeneration, trauma, infection; rarely vasculitidies
    - Mostly extrahepatic – 60% CHA, 30% RHA, 5% LHA
- Pseudoaneurysm etiologies:
    - Trauma, transhepatic biliary drainage, cholecystectomy, hepatectomy, or LT
- Male > female (2:1)
- Often identified incidentally on cross-sectional imaging (CT best)



Hepatic artery aneurysm

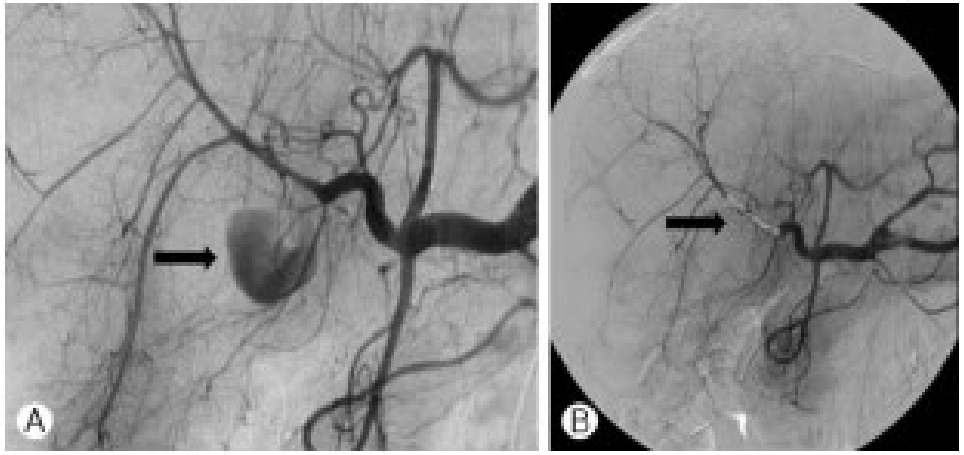


Fig. 2. (A) Arterial angiography shows the right hepatic artery aneurysm (arrow). (B) Successful embolization (arrow) of the proximal right hepatic artery aneurysm using 8 microcoils.

- Rupture rare now (esp if < 2.5cm) and symptoms depend on site and/or proximity to biliary tree or portal vein
    - >30% mortality with rupture
- Management
    - Early elective therapy preferred to minimize rupture risk
        - Particularly if diameter >2cm, expanding >0.5cm/yr during observation, pregnant or woman of child-bearing potential, LT candidate
        - Open surgical vs. endovascular
    - Observation if high-risk patient
- Paucity of data on appropriate surveillance modality and intervals; do not need follow-up for pseudoaneursysms treated with embolization

Kim GA et al. YUJM 2012; Simonetto DA et al. Am J Gastroenterol 2020.

Splenic artery aneurysm

- More commonly true aneurysm, often located distally near spleen
- Females >> males, relationship w/ multiparity
- Associations with pregnancy, portal HTN, and pancreatitis – likely detection bias given need for frequent imaging
- Etiologies: arteriosclerosis and fibromuscular dysplasia
- Typically asymptomatic / incidental but can present with gastric penetration and GIB or rupture into peritoneum
- Risk of rupture low, particularly if <2cm
- Diagnosis typically made by US or cros-sectional imaging
- Treatment parameters similar to hepatic artery aneurysm
    - Pre-emptive treatment usually recommended for pregnant women or those planning on becoming pregnant

Take-Home Points

- “Rebalanced” hemostasis in chronic liver disease – high propensity to clot and bleed
- Avoid over-transfusion and reliance on typical markers of coagulation in patients with liver disease
- PVT: **think of the 5 Ws** (who, what, when, where, why) to guide management. Efficacy and safety data on DOAC use in PVT is emerging. May still be TIPS candidates, particularly at specialized centers.
- PVT or HVT (Budd-Chiari) in the patient without cirrhosis – think thrombophilia
- Sinusoidal obstruction syndrome (SOS) – seen after allogenic stem cell transplant; UDCA as prophylaxis and defibrotide for severe cases
- Liver vascular malformations (LVMs) in Hereditary Hemorrhagic Telangiectasia (HHT) are common and type of shunt dictates the complication(s) seen. May recur post-transplant.
- Hepatic and splenic artery aneurysms – define if true aneurysm vs. pseudoaneurysm; warrant pre-emptive treatment if seen in a woman of child-bearing potential (or pregnant)

Thank you!

Questions?

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