Session 6: Consensus Statements – Vascular Diseases of the Liver in Cirrhotic and Noncirrhotic Portal Hypertension

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Etiological Workup in Primary Thrombosis of the Portal Venous System or Hepatic Venous Outflow Tract

- Close collaboration with hematologists is suggested for complete workup for prothrombotic factors including inherited and acquired thrombophilic factors, PNH, and autoimmune disorders (5;D).
- Myeloproliferative neoplasia (MPN) should be investigated in all adult patients, first by testing for V617F JAK2 mutation in peripheral blood (2b; B).

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- When V617F JAK2 is undetectable, further tests for MPN (including somatic calreticulin) may detect additional cases of JAK2-negative MPN (2b;B).
- Irrespective of peripheral blood cell counts, bone marrow biopsy is recommended for the diagnosis of MPN in patients without any biomarker of MPN. Bone marrow biopsy may be useful for the characterization of the subtype of MPN in patients with any positive biomarker (2b; B).

Use of Anticoagulants and Antiplatelet Drugs in Vascular Liver Diseases

- Low molecular weight heparin (LMWH) and vitamin K antagonists (VKA) are widely accepted and used in primary thrombosis of the portal venous system or hepatic venous outflow tract [1b; A].
- No current recommendation can be made on direct oral anticoagulants (DOACs) and antiplatelet drugs due to limited data [5;D].

Anticoagulation and Portal Vein Thrombosis (PVT) in Cirrhosis

- Screening for PVT is indicated in patients on the waiting list for liver transplant (LT) every 6 months (5;D).
- Occurrence of PVT in the presence of HCC does not imply vascular malignant invasion, but further imaging is recommended (5;D).
- Anticoagulation should be considered in potential candidates with thrombosis of the main portal vein trunk or progressive PVT (3a;B).
- In this setting, the goal is to permit/facilitate LT and reduce posttransplant mortality/morbidity, and anticoagulation should be maintained until transplantation to prevent re-thrombosis (4;C).
- In untreated potential LT candidates with PVT, an imaging follow-up every 3 months is recommended. Anticoagulation is recommended in case of progression (5;D).
- In noncandidates to LT, no recommendation regarding anticoagulation treatment can be made at present. Anticoagulation could be considered in selected cases (extension to superior mesenteric vein, known "strong" prothrombotic conditions) (5;D).
- Patients with low platelet count (e.g., $<50 \times 10^9$/L) are at higher risk of both PVT and bleeding complications under anticoagulation and require more caution (5;D).
- The benefit/risk ratio of anticoagulation for preventing or treating PVT in cirrhotic patients requires further randomized controlled trials (RCTs) (5;D).
- LMWH and VKA appear to be equally effective in cirrhotic individuals with PVT (5;D). Data on DOACs are scarce. There is an urgent need for improved tools for monitoring anticoagulation in cirrhotic patients. Measurement of thrombin generation might be an option (5; D).

Budd-Chiari Syndrome (BCS)/Hepatic Venous Outflow Tract Obstruction (HVOTO)

Definition

- Hepatic venous outflow tract obstruction (HVOTO) also known as Budd-Chiari syndrome (BCS) is the consequence of obstruction to hepatic venous outflow.
- BCS/HVOTO can be located from the level of the small hepatic veins to the level of the termination of inferior vena cava into the right atrium.
- BCS/HVOTO is a heterogeneous condition with regard to causes and pathogenesis.
- BCS/HVOTO is considered secondary when the mechanism for HVOTO is compression/invasion by a benign or malignant tumors, abscess, or cyst.
- BCS/HVOTO is considered primary otherwise.

Diagnosis

- BCS/HVOTO is diagnosed by the demonstration of an obstruction of the venous lumen or by the presence of hepatic vein collaterals (2b;B).
- Liver biopsy is not necessary to make a diagnosis of BCS/HVOTO when vascular imaging has demonstrated obstruction of the hepatic venous outflow tract (4;C).
- Liver biopsy is the only means to make a diagnosis of BCS/HVOTO of the small intrahepatic veins (4;C).
- Hepatic nodules are frequent and most often are benign. However, HCC may occur, and therefore patients should be monitored with periodic imaging and alpha-fetoprotein measurements and referred to centers experienced in managing BCS/HVOTO (2a;B).

Management

- Management of BCS/HVOTO should be undertaken using a stepwise approach including anticoagulation, angioplasty/thrombolysis, TIPS, and OLT at experienced centers (3b;B).
- Long-term anticoagulation should be given to all patients, although there is no definitive evidence for patients without identified risk factors (5;D).
- Portal hypertension should be treated since it is the major risk factor for bleeding, while excess anticoagulation plays a secondary role (4;C).
- Complications of portal hypertension should be treated as recommended for the other types of liver diseases (4;C).
- Previous bleeding related to portal hypertension is not considered a major contraindication for anticoagulation, provided that appropriate prophylaxis for recurrent bleeding is initiated (4;C).

- Stenoses that are amenable to percutaneous angioplasty/stenting (short-length stenoses) should be actively looked for and treated accordingly (5;D).
- TIPS insertion should be attempted by experts when angioplasty/stenting is not feasible and when the patient does not improve on medical therapy (4;C).
- BCS-TIPS Prognostic Index score may predict outcome in patients with TIPS (3b;B).
- Patients with high BCS-TIPS Prognostic Index score (≥7) are likely to have poor outcome following TIPS, and OLT should be considered (3b;B).
- Liver transplantation should be considered in patients with manifestations refractory to the above procedures (5;D).

Extrahepatic Portal Vein Obstruction (EHPVO)

Definition

- EHPVO is the obstruction of the extrahepatic portal vein, with or without involvement of the intrahepatic portal veins or other segments of the splanchnic venous axis. It does not include isolated thrombosis of splenic vein or superior mesenteric vein (SMV).
- EHPVO is characterized by features of recent thrombosis or of portal hypertension with portal cavernoma as a sequel of portal vein obstruction.
- Presence of cirrhosis, other underlying liver diseases (i.e., noncirrhotic portal hypertension), and/or malignancy should be ruled out. EHPVO in those situations should be considered as different entities.

Diagnosis

- EHPVO is diagnosed by Doppler US, CT, or MRI angiography, which demonstrate portal vein obstruction, presence of solid intraluminal material, or portal vein cavernoma (2a;B).
- Doppler US should be considered as first-line investigation, and CT or MRI angiography should be performed subsequently for the assessment of thrombosis extension and of potential local factors.
- EHPVO in adults is frequently associated with one or more risk factors for thrombosis, which may be occult at presentation and should be investigated (3a;B).
- Liver biopsy and HVPG are recommended, if the liver is dysmorphic on imaging or liver tests are persistently abnormal, to rule out cirrhosis or idiopathic noncirrhotic portal hypertension (1b;B). Liver stiffness by TE may be useful to exclude cirrhosis (5;D).

Anticoagulation in recent EHPVO

- Recent EHPVO rarely resolves spontaneously (3a,A).
- Low molecular weight heparin should be started immediately followed by oral anticoagulant therapy (2b;B). Most patients treated with early anticoagulation have a good clinical outcome. Therefore, even failure of recanalization do not warrant further interventions (e.g., local thrombolysis) in most cases (2b;B).
- Anticoagulation should be given for at least 6 months. When an underlying persistent prothrombotic state has been documented, long-term anticoagulation is recommended (1b;A).
- Antibiotic therapy should be given if there is any evidence of SIRS/infection (5;D).
- In patients with persistent abdominal pain, bloody diarrhea, and lactic acidosis, the risk of intestinal infarction and organ failure is increased, and recanalization and surgical intervention should be considered (3b;B).

Anticoagulation in Chronic EHPVO

- In patients without underlying prothrombotic disease, there is scarce information to recommend anticoagulant therapy (5;D).
- In patients with a persistent documented prothrombotic state, recurrent thrombosis or intestinal infarction long-term anticoagulant therapy is recommended (3b;B).
- Anticoagulation should be started after adequate portal hypertensive bleeding prophylaxis has been initiated (5;D).

Treatment of Portal Hypertension in EHPVO

- All patients in whom thrombosis has not been recanalized should be screened for gastroesophageal varices within 6 months of the acute episode. In the absence of varices, endoscopy should be repeated at 12 months and 2 years thereafter (5;D).
- There is insufficient data on whether beta-blockers or endoscopic therapy should be preferred for primary prophylaxis. Thus, guidelines for cirrhosis should be applied (5;D).
- For the control of acute variceal bleeding, endoscopic therapy is effective (1a;A).
- Evidence suggest that beta-blockers are as effective as endoscopic ligation therapy for secondary prophylaxis (2b;B).
- Mesenteric-left portal vein bypass (Meso-Rex operation) should be considered in all children with complications of chronic EHPVO, who should be referred to centers with experience in treating this condition (5;D).

Idiopathic Portal Hypertension/Noncirrhotic Portal Fibrosis/ Idiopathic Noncirrhotic Portal Hypertension (IPH, NCPF, INCPH)

- Idiopathic portal hypertension, noncirrhotic portal fibrosis, and idiopathic noncirrhotic portal hypertension indicate the same clinical entity (5;D). This includes the histological diagnosis of obliterative portal venopathy.

Diagnosis of IPH/NCPF/INCPH

- Diagnosis requires the exclusion of cirrhosis and other causes of noncirrhotic portal hypertension (2b;B).
- A liver biopsy is mandatory and HVPG is recommended for the diagnosis (2b;B).
- Immunological diseases and prothrombotic disorders should be screened (5;D).

Management of IPH/NCPF/INCPH

- There is insufficient data on which therapy should be preferred for portal hypertension prophylaxis. Management according to cirrhosis guidelines is recommended (5;D).
- Screening for the development of portal vein thrombosis. There is no data on the best screening method and interval. Doppler ultrasound at least every 6 months is suggested (5;D).
- In those patients that develop portal vein thrombosis, anticoagulant therapy should be started (5;D).

Research Agenda

- Further etiological investigations using whole genome sequencing in primary thrombosis of the portal venous system or hepatic venous outflow tract.
- Role of PVT in the course of liver cirrhosis.
- Identify risk factors for PVT in cirrhosis.
- The benefit/risk ratio of anticoagulation for preventing or treating PVT in cirrhotic patients requires further RCTs.
- Improved tools for monitoring anticoagulation in cirrhotic patients.
- Efficacy and safety of the new oral anticoagulants in patients with vascular disorders of the liver, either with cirrhosis or not.
- Role of antiplatelet drugs as add-on antithrombotic treatment.
- Role of anticoagulation and other treatments in chronic EHPVO.
- Further characterization and treatment of IPH/NCPF/INCPH.