

# Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension

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Portal hypertension is the haemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastroesophageal varices. Variceal bleeding is a medical emergency associated with a mortality that, in spite of recent progress, is still in the order of 10–20% at 6 weeks. The evaluation of diagnostic tools and the design and conduct of good clinical trials for the treatment of portal hypertension have always been difficult. Awareness of these difficulties has led to the organisation of a series of consensus meetings. The first one was organised by Andrew Burroughs in Groningen, the Netherlands in 1986 [1]. After Groningen, other meetings followed, in Baveno, Italy in 1990 (Baveno I) [2], and in 1995 (Baveno II) [3,4], in Milan, Italy in 1992 [5], in Reston, U.S.A. [6] in 1996, in Stresa, Italy, in 2000 (Baveno III) [7,8], again in Baveno in 2005 (Baveno IV) [9,10], in Atlanta in 2007 [11], and again in Stresa in 2010 (Baveno V) [12,13].

The aims of these meetings were to develop definitions of key events in portal hypertension and variceal bleeding, to review the existing evidence on the natural history, the diagnosis and the therapeutic modalities of portal hypertension, and to issue evidence-based recommendations for the conduct of clinical trials and the management of patients. All these meetings were successful and produced consensus statements on some important points, although several issues remained unsettled.

To continue the work of the previous meetings, a Baveno VI workshop was held on April 10–11, 2015. The workshop was attended by many of the experts responsible for most of the major achievements of the last years in this field. Many of them had attended the previous meetings as well.

A concept that has gained wide acceptance over the past few years is the fact that patients in different stages of cirrhosis have different risks of developing complications and of dying. Accordingly, the Baveno VI workshop was entitled “Stratifying

risk and individualizing care for portal hypertension”. The main fields of discussion were the use of invasive and non-invasive methods for the screening and surveillance of gastroesophageal varices and of portal hypertension, the impact of aetiological therapy for cirrhosis, the primary prevention of decompensation, the management of the acute bleeding episode, the prevention of recurrent haemorrhage and other decompensating events, and vascular diseases of the liver in cirrhotic and non-cirrhotic patients. For each of these topics, a series of consensus statements were discussed and agreed upon. Whenever applicable, the level of existing evidence was evaluated and the recommendations were ranked according to the Oxford System [14] (i.e., level of evidence from 1 = highest to 5 = lowest; grade of recommendation from A = strongest, to D = weakest). The presentations given during the workshop are reported ‘in extenso’ in the Baveno VI proceedings [15]. A summary of the most important conclusions is reported here. Whenever relevant, the changes from previous consensus statements are outlined. The areas where major new recommendations were made are: screening and surveillance, the importance of obesity, comorbidities and malnutrition, the use of beta blockers in patients with refractory ascites/end-stage liver disease, and anticoagulation and portal vein thrombosis in liver cirrhosis.

## Definitions of key events regarding the bleeding episode (changed from Baveno V)

- Six-week mortality should be the primary endpoint for studies for treatment of acute variceal bleeding (5;D).
- 5 day treatment failure is defined using Baveno IV/V criteria without ABRI (adjusted blood requirement index) and with a clear definition of hypovolemic shock (1b;A).
- Baveno IV/V criteria correlate with 6-week mortality (1b;A) and should be included in future studies as a secondary endpoint to allow further validation (5;D).
- Additional endpoints should be reported including: need for salvage therapy (tamponade, additional endoscopic therapy, transjugular intrahepatic portosystemic shunt [TIPS], surgery etc.); blood transfusion requirements and days of ICU/hospital stay (5;D).

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## Position Paper

### Screening and surveillance: Invasive and non-invasive methods (changed from Baveno III-V)

#### Definition of compensated advanced chronic liver disease (new)

- The introduction of transient elastography (TE) in clinical practice has allowed the early identification of patients with chronic liver disease (CLD) at risk of developing clinically significant portal hypertension (CSPH) (1b;A).
- For these patients, the alternative term “compensated advanced chronic liver disease (cACLD)” has been proposed to better reflect that the spectrum of severe fibrosis and cirrhosis is a continuum in asymptomatic patients, and that distinguishing between the two is often not possible on clinical grounds (5;D).
- Currently, both terms: “cACLD” and “compensated cirrhosis” are acceptable (5;D).
- Patients with suspicion of cACLD should be referred to a liver disease specialist for confirmation, follow-up and treatment (5;D).

#### Criteria to suspect cACLD (new)

- Liver stiffness by TE is sufficient to suspect cACLD in asymptomatic subjects with known causes of CLD (1b;A).
- TE often has false positive results; hence two measurements on different days are recommended in fasting conditions (5;D).
- TE values <10 kPa in the absence of other known clinical signs rule out cACLD; values between 10 and 15 kPa are suggestive of cACLD but need further test for confirmation; values >15 kPa are highly suggestive of cACLD (1b;A).

#### Criteria to confirm cACLD (new)

- Invasive methods are employed in referral centres in a stepwise approach when the diagnosis is in doubt or as confirmatory tests
- Methods and findings that confirm the diagnosis of cACLD are:
  - Liver biopsy showing severe fibrosis or established cirrhosis (1a;A).
  - Collagen proportionate area (CPA) measurement on histology provides quantitative data on the amount of fibrosis and holds prognostic value (2b;B) and its assessment is recommended (5;D).
  - Upper GI endoscopy showing gastroesophageal varices (1b;A).
  - Hepatic venous pressure gradient (HVPG) measurement; values >5 mmHg indicate sinusoidal portal hypertension (1b;A).

#### Diagnosis of CSPH in patients with cACLD (new)

- HVPG measurement is the gold-standard method to assess the presence of CSPH, which is defined as HVPG  $\geq 10$  mmHg (1b;A).

- By definition, patients without CSPH have no gastroesophageal varices, and have a low five year risk of developing them (1b;A).
- In patients with virus related cACLD non-invasive methods are sufficient to rule-in CSPH, defining the group of patients at risk of having endoscopic signs of PH. The following can be used (2b;B):
  - Liver stiffness by TE ( $\geq 20$ –25 kPa; at least two measurements on different days in fasting condition; caution should be paid to flares of ALT; refer to EASL guidelines for correct interpretation criteria), alone or combined to platelets and spleen size.
- The diagnostic value of TE for CSPH in other aetiologies remains to be ascertained (5;D).
- Imaging showing collateral circulation is sufficient to rule-in CSPH in patients with cACLD of all aetiologies (2b;B).

#### Identification of patients with cACLD who can safely avoid screening endoscopy (new)

- Patients with a liver stiffness <20 kPa and with a platelet count >150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy (1b;A).
- These patients can be followed up by yearly repetition of TE and platelet count (5;D).
- If liver stiffness increases or platelet count declines, these patients should undergo screening esophagogastroduodenoscopy (5;D).

#### Surveillance of oesophageal varices (changed from Baveno V)

- In compensated patients with no varices at screening endoscopy and with ongoing liver injury (e.g. active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at 2 year intervals (5;D).
- In compensated patients with small varices and with ongoing liver injury (e.g. active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at one year intervals (5;D).
- In compensated patients with no varices at screening endoscopy in whom the aetiological factor has been removed (e.g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors (e.g. obesity), surveillance endoscopy should be repeated at three year intervals (5;D).
- In compensated patients with small varices at screening endoscopy in whom the aetiological factor has been removed (e.g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors (e.g. obesity), surveillance endoscopy should be repeated at two year intervals (5;D).

#### Cost considerations (new)

- Whatever policy and method is adopted for screening and surveillance, cost should be taken into account in future studies (5;D).

Research agenda

- Future studies should explore the possibility to stop surveillance after two controls showing no varices.
- Long-term data are needed concerning the benefits of screening and surveillance programs.

**Impact of aetiological therapy (new)**

- Management of patients with cirrhosis should focus on preventing the advent of all complications while in the compensated phase (1b;A).
- Due to different prognosis, patients with compensated cirrhosis should be divided in those with and without CSPH (1b;A). The goal of treatment in the first is to prevent CSPH while in the second is to prevent decompensation.
- The concept of CSPH is HVPG-driven and cannot completely be substituted at present by non-invasive tools (1b;A).
- Aetiological treatment of the underlying liver disease may reduce portal hypertension and prevents complications in patients with established cirrhosis (1b;A) (unchanged).
- HVPG change is an acceptable surrogate of clinical outcome in patients with non-cholestatic cirrhosis (2b;B). An HVPG change of 10% or more is to be considered significant (1b;A).
- Obesity worsens the natural history of compensated cirrhosis of all aetiologies (1b;A). A lifestyle modification with diet and exercise decreases body weight and HVPG in cirrhosis with obesity (2b;B).
- Alcohol abstinence should be encouraged in all patients with cirrhosis irrespective of aetiology (2b;B).
- The clinical use of statins is promising and should be evaluated in further phase III studies (1b;A).

Research agenda

- Studies should focus on tools, either invasive (e.g. quantitative fibrosis assessment with CPA) and/or preferably non-invasive (e.g. elastography, biomarkers, or combinations or other means), to predict/select patients at risk of decompensation in liver diseases of different aetiology.
- Anti-fibrotic strategies and approaches to target, amongst others, the coagulation system, FXR-pathway, renin-angiotensin system, angiogenesis and the gut-liver axis, should be further explored for prevention of decompensation in patients with cirrhosis and CSPH.

**Changing scenarios: Prevention of decompensation (partly changed from Baveno V)**

*Cure of the etiologic agent*

- Successful cure of the etiologic agent in CLD may improve both liver structure and function, and this could translate into a portal pressure reduction (1b;A).

*Comorbidities and malnutrition (new)*

- Comorbidities (obesity, diabetes, cancer, osteoporosis, pulmonary, renal and cardiovascular diseases) are frequently present in patients with compensated cirrhosis. Some of them can contribute to decompensation, while others are a consequence of liver disease (2b;B).
- Malnutrition and sarcopenia have been shown to have an impact on hepatic encephalopathy, development of ascites, incidence of infections and survival in cirrhotic patients (1b;A). As the evidence was mainly reported in decompensated patients further studies are needed to draw definitive conclusions on this topic also in patients with compensated cirrhosis (5;D).

*Patients with no varices or small varices (unchanged)*

- There is no indication, at this time, to use beta blockers to prevent the formation of varices (1b;A).
- Patients with small varices with red wale marks or Child-Pugh C class have an increased risk of bleeding (1b;A) and should be treated with non-selective beta blockers (NSBB) (5;D).
- Patients with small varices without signs of increased risk may be treated with NSBB to prevent bleeding (1b;A). Further studies are required to confirm their benefit.

*Patients with medium-large varices (unchanged)*

- Either NSBB or endoscopic band ligation is recommended for the prevention of the first variceal bleeding of medium or large varices (1a;A).
- The choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events (5;D).

*Carvedilol (changed from Baveno V)*

- Traditional NSBB (propranolol, nadolol) (1a;A) and carvedilol (1b;A) are valid first line treatments.
- Carvedilol is more effective than traditional NSBB in reducing HVPG (1a;A) but has not been adequately compared head-to-head to traditional NSBB in clinical trials.

*Patients with gastric varices (changed from Baveno V)*

- Although a single study suggested that cyanoacrylate injection is more effective than beta blockers in preventing first bleeding in patients with large gastroesophageal varices type 2 or isolated gastric varices type 1 (1b;A), further studies are needed to evaluate the risk/benefit ratio of using cyanoacrylate in this setting before a recommendation can be made (5;D).

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### Role of HVPG measurement (changed from Baveno V)

- The decision to treat with beta blockers should be taken when indicated, independent of the possibility of measuring HVPG (1a;A).
- HVPG measurement provides prognostic information (1b;A).
- HVPG change is a relevant surrogate outcome (1b;A).
- Measurement of HVPG response to therapy offers additional relevant information: a decrease in HVPG of at least 10% from baseline or to  $\leq 12$  mmHg after chronic treatment with NSBB is clinically relevant in the setting of primary prophylaxis (1b;A). Similarly, acute HVPG response to intravenous propranolol may be used to identify responders to beta blockers, specifically a decrease in HVPG of 10% or to  $\leq 12$  mmHg may be relevant in this setting (1b;A).
- HVPG response to NSBBs is associated with a significant reduction in risk of variceal bleeding (1a;A) and decompensation (1b;A).
- HVPG measurements should be encouraged in clinical trials investigating novel therapies, but are not essential if portal hypertension-associated endpoints are well defined (5;D).

### Use of NSBB in patients with end-stage liver disease (new)

- The safety of NSBB in subgroups with end-stage disease (refractory ascites and/or spontaneous bacterial peritonitis) has been questioned (2b;B).
- NSBB contraindications may be absent when the therapy is firstly prescribed but need to be monitored during the evolution of the disease (5;D).
- Close monitoring is necessary in patients with refractory ascites, and reduction of dose or discontinuation can be considered in those who develop low blood pressure and impairment in renal function (4;C).
- If NSBB are stopped endoscopic band ligation should be performed (5;D).

### Research agenda

- More data are needed to unravel the course of disease after cure of the aetiological factor.
- Successful treatment of the underlying liver disease (alcohol abstinence, antiviral therapy) may reduce HVPG, size of varices and risk of bleeding. Novel antivirals are expected to expand this knowledge and reinforce data to suggest changes in surveillance intervals of varices and other complications.
- Competing risks from comorbidities should be taken into account in future studies.
- Future studies are required to describe the impact of early detection and treatment of comorbidities.
- The impact of treatments to improve nutritional status on prognosis and mortality should be evaluated.
- New prospective studies to assess the safety of NSBB in end-stage disease are warranted.

### Management of the acute bleeding episode (partly changed from Baveno V)

#### Blood volume restitution (unchanged from Baveno V)

- The goal of resuscitation is to preserve tissue perfusion. Volume restitution should be initiated to restore and maintain hemodynamic stability.
- Packed red blood cells transfusion should be done conservatively at a target haemoglobin level between 7 and 8 g/dl, although transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status and ongoing bleeding (1b;A).
- Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data (5;D).
- PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis (1b;A).

#### Antibiotic prophylaxis (partly changed from Baveno V)

- Antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal (GI) bleeding and should be instituted from admission (1a;A).
- The risk of bacterial infection and mortality are very low in patients with Child-Pugh A cirrhosis (2b;B), but more prospective studies are needed to assess whether antibiotic prophylaxis can be avoided in this subgroup of patients.
- Individual patient risk characteristics and local antimicrobial susceptibility patterns must be considered when determining appropriate first line acute variceal haemorrhage antimicrobial prophylaxis at each centre (5;D).
- Intravenous ceftriaxone 1 g/24 h should be considered in patients with advanced cirrhosis (1b;A), in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis (5;D).

#### Prevention of hepatic encephalopathy (changed from Baveno V)

- Recent studies suggest that either lactulose or rifaximin may prevent hepatic encephalopathy in patients with cirrhosis and upper GI bleeding (1b;A). However, further studies are needed to evaluate the risk/benefit ratio and to identify high risk patients before a formal recommendation can be made (5;D).
- Although, there are no specific studies in acute variceal bleeding, it is recommended to adopt the recent EASL/AASLD HE guidelines which state that episodic HE should be treated with lactulose (25 ml q 12 h until 2–3 soft bowel movements are produced, followed by dose titration to maintain 2–3 soft bowel movements per day) (5;D).

## Assessment of prognosis (unchanged from Baveno V)

- Child-Pugh class C, the updated MELD score, and failure to achieve primary haemostasis are the variables most consistently found to predict six week mortality (2b;B).

## Pharmacological treatment (partly changed from Baveno V)

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before endoscopy (1b;A).
- Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy and continued for up to five days (1a;A).
- Hyponatremia has been described in patients under terlipressin, especially in patients with preserved liver function. Therefore, sodium levels must be monitored (1b;A).

## Endoscopy (changed from Baveno V)

- Following hemodynamic resuscitation, patients with upper GI bleeding and features suggesting cirrhosis should undergo esophagogastroduodenoscopy within 12 h of presentation (5;D).
- In the absence of contraindications (QT prolongation), pre-endoscopy infusion of erythromycin (250 mg IV 30–120 min before endoscopy) should be considered (1b;A).
- The availability both of an on-call GI endoscopist proficient in endoscopic haemostasis and on-call support staff with technical expertise in the usage of endoscopic devices enables performance of endoscopy on a 24/7 basis and is recommended (5;D).
- Patients with acute variceal haemorrhage should be considered for ICU or other well monitored units (5;D).
- In patients with altered consciousness, endoscopy should be performed with protection of the airway (5;D).
- Ligation is the recommended form of endoscopic therapy for acute oesophageal variceal bleeding (1b;A).
- Endoscopic therapy with tissue adhesive (e.g. N-butylcyanoacrylate) is recommended for acute bleeding from isolated gastric varices (IGV) (1b;A) and those gastroesophageal varices type 2 (GOV2) that extend beyond the cardia (5;D).
- To prevent rebleeding from gastric varices, consideration should be given to additional glue injection (after two to four weeks), beta-blocker treatment or both combined or TIPS (5;D). More data in this area are needed.
- EVL or tissue adhesive can be used in bleeding from gastroesophageal varices type 1 (GOV1) (5;D).

## Early TIPS placement (changed from Baveno V)

- An early TIPS with PTFE-covered stents within 72 h (ideally <24 h) must be considered in patients bleeding from EV, GOV1 and GOV2 at high risk of treatment failure (e.g. Child-Pugh class C <14 points or Child-Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy (1b;A). Criteria for high risk patients should be refined.

## Balloon tamponade (changed from Baveno V)

- Balloon tamponade, given the high incidence of its severe adverse events, should only be used in refractory oesophageal bleeding, as a temporary “bridge” (for a maximum of 24 h) with intensive care monitoring and considering intubation, until definitive treatment can be instituted (5;D).

## Use of self-expandable metal stents (changed from Baveno V)

- Data suggest that self-expanding covered oesophageal metal stents may be as efficacious and a safer option than balloon tamponade in refractory oesophageal variceal bleeding (4;C).

## Management of treatment failures (unchanged from Baveno V)

- Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by PTFE-covered TIPS (2b;B).
- Rebleeding during the first five days may be managed by a second attempt at endoscopic therapy. If rebleeding is severe, PTFE-covered TIPS is likely the best option (2b;B).

## Research agenda

- Trials of preventative strategies in acute kidney injury in variceal bleeding should be undertaken.
- Treatment and prevention of HE.
- Optimal use of glue obliteration in gastric variceal bleeding.
- Role of endoscopic ultrasound in variceal injection therapy.
- Alternative endoscopic haemostasis techniques in EVB, e.g., haemostatic powders.
- Improve prognostic models: Better stratification of risk to determine applicability of updated MELD or other potential new models to improve stratification of risk to determine type of treatment.
- Applicability of models to determine other issues such as timing of the initial endoscopy, duration of the drug therapy and type of treatment.
- Use of early TIPS in gastric varices.
- Use of balloon occluded retrograde transvenous obliteration (BRTO) in IGV.

## Preventing recurrent variceal haemorrhage and other decompensating events (changed from Baveno V)

### Prevention of recurrent variceal haemorrhage (changed from Baveno V)

- First line therapy for all patients is the combination of NSBB (propranolol or nadolol) + EVL (1a;A).
- EVL should not be used as monotherapy unless there is intolerance/ contraindications to NSBB (1a;A).

## Position Paper

- NSBB should be used as monotherapy in patients with cirrhosis who are unable or unwilling to be treated with EVL (1a;A).
- Covered TIPS is the treatment of choice in patients that fail first line therapy (NSBB + EVL) (2b;B).
- Because carvedilol has not been compared to current standard of care, its use cannot be recommended in the prevention of rebleeding (5;D).

### Secondary prophylaxis in patients with refractory ascites (new)

- In patients with cirrhosis and refractory ascites [16] NSBB (propranolol, nadolol) should be used cautiously with close monitoring of blood pressure, serum sodium and serum creatinine (4;C).
- Until randomized trials are available NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events (5;D):
  - Systolic blood pressure <90 mmHg
  - Hyponatremia (<130 mEq/L)
  - Acute kidney injury [17]
- [This assumes that drugs that could precipitate these events (e.g. NSAIDs, diuretics) have been removed].
- The consequences of discontinuing NSBB in the setting of secondary prophylaxis are unknown.
- If there was a clear precipitant for these events (e.g. spontaneous bacterial peritonitis, haemorrhage), reinitiation of NSBB should be considered after these abnormal parameters return to baseline values after resolution of the precipitant (5;D).
- If reinitiating NSBBs, dose should be re-titrated, starting at the lowest dose (5;D)
- If the patient continues to be intolerant to NSBB and is an appropriate TIPS candidate, covered TIPS placement may be considered (5;D).

### Secondary prophylaxis of portal hypertensive gastropathy (PHG) (changed from Baveno V)

- PHG has to be distinguished from gastric antral vascular ectasia because treatments are different (4;C).
- NSBB are first line therapy in preventing recurrent bleeding from PHG (1b;A).
- TIPS might be considered in patients with transfusion-dependent PHG in whom NSBB and/or endoscopic therapies fail (4;C).

### Trial Design (new)(5;D)

- Primary endpoints in patients after variceal haemorrhage depend on the presence of other complications (ascites, encephalopathy, jaundice):
  - Patients without additional complications (low risk of death): endpoint should be development of an additional complication, including variceal rebleeding
  - Patients with an additional complication (high risk of death): endpoint should be mortality

- The use of “all-cause rebleeding” is a good strategy to minimize bias in definition of rebleeding.
- Patients in these trials should be randomized five to ten days after the index bleed.
- HVPG response assessment is needed as a surrogate marker in trials where a low rate of events is expected.
- Sample size and outcomes should be assessed by using competing risk analyses in settings where transplant rates are predictably high.
- The impact of comorbidities and successful treatment of the underlying aetiology on disease progression and mortality requires further evaluation.

### Research agenda

- Efficacy/safety assessment of promising drugs (statins, FXR agonists, anticoagulants and rifaximin) and nutritional optimization.
- HVPG-guided therapy.
- Role of covered TIPS as first line therapy after variceal bleeding (secondary prophylaxis).
- Non-invasive predictors of drug response.
- Effect of current therapies on patient-reported outcomes, particularly in low-mortality patients.
- Innovative trials for small subpopulations of patients who have bled from varices (e.g. children, fundal varices, hepatocellular carcinoma (HCC), patients who have bled while on NSBB prophylaxis).

### Vascular diseases of the liver in cirrhotic and non-cirrhotic portal hypertension (changed from Baveno V)

#### Aetiological work-up in primary thrombosis of the portal venous system or hepatic venous outflow tract

- Close collaboration with haematologists is suggested for complete work-up for prothrombotic factors including inherited and acquired thrombophilic factors, paroxysmal nocturnal haemoglobinuria (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).
- 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 bio-marker of MPN. Bone marrow biopsy may be useful for the characterization of the subtype of MPN in patients with any positive bio-marker (2b;B).

#### Use of anticoagulants and anti-platelet drugs in vascular liver diseases

- Low Molecular Weight Heparin and Vitamin K Antagonists 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 and anti-platelet 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 six months (5;D).
- Occurrence of PVT in 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 post-transplant 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 three months is recommended. Anticoagulation is recommended in case of progression (5;D).
- In non-candidates 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).
- Low molecular weight heparin and vitamin K antagonists appear to be equally effective in cirrhotic individuals with PVT (5;D). Data on direct oral anticoagulants 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/Hepatic venous outflow tract obstruction*

*Definition (unchanged from Baveno V)*

- 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 regards to causes and pathogenesis.
- BCS/HVOTO is considered secondary when the mechanism for HVOTO is compression/invasion by a benign or malignant tumour, abscess or cyst.
- BCS/HVOTO is considered primary otherwise.

*Diagnosis (partly changed from Baveno V)*

- 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 benign. However HCC may occur and therefore patients should be monitored with periodic imaging and alpha-fetoprotein measurements and referred to centres experienced in managing BCS/HVOTO (2a;B).

*Management (partly changed from Baveno V)*

- Management of BCS/HVOTO should be undertaken using a stepwise approach including anticoagulation, angioplasty/thrombolysis, TIPS and orthotopic liver transplantation at experienced centres (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 contra-indication for anticoagulation, provided 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 ( $\geq 7$ ) are likely to have poor outcome following TIPS and orthotopic liver transplantation 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 (partly changed from Baveno V)*

- 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.

## Position Paper

- 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. non-cirrhotic portal hypertension) and/or malignancy should be ruled out. EHPVO in those situations should be considered as different entities.

### Diagnosis (changed from Baveno V)

- EHPVO is diagnosed by Doppler ultrasound, CT- or MRI-angiography, which demonstrate portal vein obstruction, presence of solid intraluminal material or portal vein cavernoma (2a;B).
- Doppler ultrasound should be considered first line investigation and CT- or MRI-angiography should be performed subsequently for assessment of thrombosis extension and of potential local factors (2a;B).
- 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 non-cirrhotic portal hypertension (1b;B). Liver stiffness by TE may be useful to exclude cirrhosis (5;D).

### Anticoagulation in recent EHPVO (changed from Baveno V)

- 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 does not warrant further interventions (e.g. local thrombolysis) in most cases (2b;B).
- Anticoagulation should be given for at least six 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 diarrhoea and lactic acidosis the risk of intestinal infarction and organ failure is increased, repermeabilization and surgical intervention should be considered (3b;B).

### Anticoagulation in chronic EHPVO (changed from Baveno V)

- 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 (partly changed from Baveno V)

- All patients in whom thrombosis has not been recanalised should be screened for gastroesophageal varices within six months of the acute episode. In the absence of varices, endoscopy should be repeated at 12 months and two 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 suggests 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 centres with experience in treating this condition (5;D).

### Idiopathic portal hypertension/non-cirrhotic portal fibrosis/idiopathic non-cirrhotic portal hypertension (new)

- Idiopathic portal hypertension (IPH), non-cirrhotic portal fibrosis (NCPF) and Idiopathic non-cirrhotic portal hypertension (INCPH) indicate the same clinical entity (5;D). This includes the histological diagnosis of obliterative portal venopathy.

### Diagnosis of IPH/NCPF/INCPH (new)

- Diagnosis requires the exclusion of cirrhosis and other causes of NCPH (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 (new)

- 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 PVT. 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 PVT anticoagulant therapy should be started (5;D).

*Research agenda*

- Further aetiological 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 or without cirrhosis.
- Role of anti-platelet drugs as add-on antithrombotic treatment.
- Role of anticoagulation and other treatments in chronic EHPVO.
- Further characterization and treatment of IPH/NCPF/INCPH.

**Other issues**

Besides the consensus sessions, five lectures were given in Baveno VI. The topics of these lectures were the concept of risk stratification, competing risks and prognostic stages of cirrhosis, the basic and clinical aspects of the relationship between the gut microbiome and cirrhosis, and the 2015 report on controversies and challenges in paediatrics. The texts of these lectures are reported in the Baveno VI proceedings book [15]. The Baveno VI Consensus Workshop was followed by a paediatric satellite meeting in which the controversies in the management of varices in children were discussed.

**Conclusions**

The consensus definitions of treatment failure in variceal bleeding have been simplified in view of the results of the evaluation of their performance in the field. The use of these definitions, as well as of the other endpoints proposed, in future studies is encouraged to provide further validation. Several statements agreed upon in previous Baveno workshops were taken for granted and not discussed in Baveno VI. Interested readers can refer to the Baveno I-V reports [2–4,7–10,12,13].

The topics listed in the research agenda reflect the opinions of the experts about the areas where new information is most needed.

**Baveno VI Faculty**

The following were members of the Baveno VI Scientific Committee: Roberto de Franchis [Milan, Italy (Chair)], Juan G Abraldes (Edmonton, Canada), Jasmohan Bajaj (Richmond, USA), Annalisa Berzigotti (Bern, Switzerland), Jaime Bosch (Barcelona, Spain), Andrew K Burroughs (London, UK)<sup>1</sup>,

Gennaro D'Amico (Palermo, Italy), Alessandra Dell'Era (Milan, Italy), Juan Carlos Garcia-Pagàn (Barcelona, Spain), Guadalupe Garcia-Tsao (West Haven, USA), Norman Grace (Boston, USA), Roberto Groszmann (New Haven, USA), Aleksander Krag (Odense, Denmark), Wim Laleman (Leuven, Belgium), Vincenzo La Mura (Milan, Italy), Didier Lebrec (Clichy, France), Gin Ho Lo (Taipei, Taiwan) Carlo Merkel (Padua, Italy), James O'Beirne (London, UK), Markus Peck (Vienna, Austria), Massimo Primignani (Milan, Italy), Francesco Salerno (Milan, Italy), Shiv K Sarin (New Delhi, India), Dominique Thabut (Paris, France), Jonel Trebicka (Bonn, Germany), Alexander Zipprich (Halle, Germany).

The following chaired sessions or lectures: Juan G Abraldes (Edmonton, Canada), Annalisa Berzigotti (Bern, Switzerland), Jaime Bosch (Barcelona, Spain), Roberto de Franchis (Milan, Italy), Juan Carlos Garcia-Pagàn (Barcelona, Spain), Guadalupe Garcia-Tsao (West Haven, USA), Norman Grace (Boston, USA), Roberto Groszmann (New Haven, USA), Aleksander Krag (Odense, Denmark), Wim Laleman (Leuven, Belgium), Didier Lebrec (Clichy, France), Carlo Merkel (Padua, Italy), Massimo Primignani (Milan, Italy), Shiv K Sarin (New Delhi, India), Dominique Thabut (Paris, France), Jonel Trebicka (Bonn, Germany).

The following participated in the presentations and the discussions as panellists in the consensus sessions: Lars Aabakken (Oslo, Norway), Augustin Albillos (Madrid, Spain), Salvador Augustin (Barcelona, Spain), Rafael Bañares (Madrid, Spain), Tom Boyer (Tucson, USA), Christophe Bureau (Toulouse, France), Laurent Castera (Clichy, France), Andrea De Gottardi (Bern, Switzerland), Alessandra Dell'Era (Milan, Italy), Angels Escorsell (Barcelona, Spain), Joan Genesca (Barcelona, Spain), Ian Gralnek (Haifa, Israel), Roberto Groszmann (New Haven, USA), Virginia Hernandez-Gea (Barcelona, Spain), Vincenzo La Mura (Milan, Italy), Frank Leebeek (Rotterdam, The Netherlands), Gin Ho Lo (Taipei, Taiwan), Manuela Merli (Rome, Italy), Richard Moreau (Clichy, France), Frederik Nevens (Leuven, Belgium), James O'Beirne (London, UK), Markus Peck (Vienna, Austria), Massimo Pinzani (London, UK), Thomas Reiberger (Boston, USA), Cristina Ripoll (Halle, Germany), Marika Rudler (Paris, France), Francesco Salerno (Milan, Italy), Shiv K Sarin (New Delhi, India), Susana Seijo (New York, USA), Puneeta Tandon (Edmonton, Canada), Emmanouil Tsochatzis (London, UK), Dominique Valla (Clichy, France), Candid Villanueva (Barcelona, Spain), Julio Vorobioff (Rosario, Argentina), Alexander Zipprich (Halle, Germany).

The following gave review lectures: Jasmohan Bajaj (Richmond, USA), Gennaro D'Amico (Palermo, Italy), Ben Shneider (Houston, USA), Jayant Talwalkar (Rochester, USA), Reiner Wiest (Bern, Switzerland).

**Conflict of interest**

The authors that have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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<sup>1</sup> Dr. Burroughs was a Faculty member but died last year.

# Position Paper

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