Journal of Hepatology 2000; **33**: 846–852
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Munksgaard · Copenhagen

Journal of Hepatology
ISSN 0168-8278

Updating Consensus in Portal Hypertension: Report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension

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Portal hypertension is the hemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastroesophageal varices. Since variceal bleeding is a medical emergency associated with significant morbidity and mortality, the evaluation of diagnostic tools and the design and conduct of good clinical trials for the treatment of this condition have always been difficult. Awareness of these difficulties has led to the organization of a series of meetings aimed at reaching consensus on the definitions of some key events related to portal hypertension and variceal bleeding, and at producing guidelines for the conduct of trials in this field. Such meetings took place in Groningen, the Netherlands in 1986 (1), in Baveno, Italy in 1990 (Baveno I) (2) and in 1995 (Baveno II) (3,4), in Milan, Italy in 1992 (5), and in Reston, USA (6), in 1996. 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 III workshop was held on 13–14 April, 2000. The workshop was attended by many of the experts responsible for most of the major achievements of recent years in this field. The majority of them had attended the Groningen, Baveno I, Baveno II and Reston meetings as well.

The main fields of discussion of the Baveno III workshop were the same as in Baveno I and II, i.e. the definitions of key events concerning the bleeding episode, the diagnostic evaluation of patients, the therapeutic options in patients with portal hypertension, and the methodological requirements for future trials in this field. For each of these topics, a series of consensus statements were discussed and agreed upon. These statements are reported *in extenso* in the Baveno III proceedings (7). A summary of the most important conclusions reached at the workshop is reported here.

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Definition of Key Events Regarding the Bleeding Episode

Active bleeding

Active bleeding at endoscopy (defined as blood emanating from a varix) has prognostic value as a predictor of failure to control bleeding in the next few days. Future studies should ascertain whether the clinical or prognostic significance of active bleeding is the same with or without drug therapy, and whether active bleeding is related to mortality.

Failure to control bleeding

At Baveno II (3,4), the definition of failure to control bleeding was divided into 2 time frames:

1) Within 6 h: any of the following factors: a) transfusion of 4 units of blood or more, and inability to achieve an increase in systolic blood pressure of 20 mmHg or to 70 mmHg or more, and/or b) pulse reduction to less than 100/min or a reduction of 20/min from baseline pulse rate.
2) After 6 h: any of the following factors: a) the occurrence of hematemesis, b) reduction in blood pressure of more than 20 mmHg from the 6-h point, and/or c) increase of pulse rate of more than 20/min from the 6-h point on 2 consecutive readings 1 h apart, d) transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the Hct to above 27% or Hb to above 9 g/dl.

These definitions were confirmed at Reston (6). At Baveno III it was felt that some of the above criteria could be misleading. There was consensus that the Baveno II (3,4) and Reston (6) criteria should be re-evaluated, in particular the use of hemodynamic criteria without evidence of clinical bleeding.

Failure of secondary prevention
Failure to prevent rebleeding was defined as a single episode of clinically significant rebleeding from portal hypertensive sources, according to the Baveno II (3,4) criteria: [transfusion requirement of 2 units of blood or more within 24 h of time zero – the time of admission of a patient to the first hospital he is taken to – (2), *together with* a systolic blood pressure <100 mmHg or a postural change of > 20 mmHg *and/or* pulse rate >100/min at time zero].

New information to be obtained in future studies
More information is needed on the relationship of infection to failure to control bleeding and mortality. Trials of salvage therapy following failure to prevent early rebleeding should be performed.

Diagnosis of Portal Hypertension

Definition of clinically significant portal hypertension (CSPH)
An increase in portal pressure gradient to a threshold above approximately 10 mm Hg. The presence of varices, variceal hemorrhage and/or ascites is indicative of the presence of CSPH.

Diagnostic tools to assess portal hypertension
The reliability of both the hepatic vein pressure gradient (HVPG) measurement and endoscopic assessment of esophageal varices for the diagnosis of CSPH is satisfactory. However, specific, simple guidelines might further improve reliability. The accuracy of non-invasive tests such as Doppler ultrasound and variceal pressure measurement for the diagnosis of CSPH should be further assessed before their use can be recommended in clinical practice.

Screening for the presence of CSPH and follow-up
a) All cirrhotic patients should be screened for the presence of varices at the time of the initial diagnosis of cirrhosis.

b) In compensated patients *without varices*, endoscopy should be repeated at 2–3-year intervals to evaluate the development of varices

c) In compensated patients *with small varices*, endoscopy should be repeated at 1–2-year intervals to evaluate progression of varices.

d) There is no indication for subsequent evaluations once large varices are detected.

The suggested intervals for follow-up endoscopy were prolonged in comparison to those agreed upon at Baveno II (3,4) and Reston (5), as dictated by the current evidence in the literature. However, the available information on this matter is scanty. Further studies of the natural course of cirrhosis should better clarify the incidence of esophago-gastric varices and the progression of variceal size from small to large, in order to better define the interval between endoscopic evaluations.

Treatment monitoring
HVPG is the only parameter presently suitable to monitor pharmacological treatment. Variceal pressure measurement and Doppler-ultrasound seem promising but, due to inter-equipment and inter-observer variability, their use in clinical practice cannot be recommended. The efficacy of treatment adjustments based on monitoring should be further investigated.

Diagnosis of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE)
1) Based on current data of natural history (8), PHG should be classified as:
   a) Mild: when mosaic-like pattern (MLP) of mild degree (without redness of the areola) is present;
   b) Severe: when the MLP is superimposed by red signs or if any other red sign is present.
   The lesions may change over time (fluctuate, worsen or improve).
2) GAVE is a distinct clinical, endoscopic and histopathologic entity endoscopically characterized by aggregates of red spots arranged in linear pattern or diffused lesion, if confirmed by biopsy, in the antrum of the stomach. GAVE can be seen in conditions other than portal hypertension.

Diagnosis of gastric varices
The classification of Sarin et al. (9) should be used. In addition, for fundal varices, the presence of red signs, large size and Child class B or C should be considered as risk factors for bleeding.

Fundal gastric varices (GOV2 and IGV1) are at the highest risk of bleeding.

Therapeutic Options in Patients with Portal Hypertension

Pre-primary prophylaxis (prevention of the formation/growth of varices)
Every patient with cirrhosis without complications of portal hypertension ideally needs HVPG measurements in order to be included in a trial of pre-primary

prevention. The sequence portal hypertension–collaterals–varices is an accepted one; collaterals can be diagnosed before the development of varices.

Portal pressure is predictive of varices formation, while the clinical importance of collaterals as predictors of more severe portal hypertensive complications should be further investigated.

"Low risk varices" are small-sized varices without red color signs. The risk of bleeding within 2 years of these varices is <10%. The risk of bleeding between two consecutive endoscopies performed at yearly intervals in patients with cirrhosis undergoing surveillance for low-risk varices is <5%. The reproducibility of a diagnosis of low-risk varices by endoscopy is variable and influenced by expertise. Spontaneous regression of small varices is a rare event. Regression is related to improvement in liver status, particularly after alcohol abstinence in alcoholic cirrhosis.

More data are needed before a conclusion can be drawn on the usefulness of starting prophylaxis of variceal bleeding in patients with low-risk varices.

Prevention of the first bleeding episode

The conclusions reached at Baveno II (3,4) and Reston (5) (i. e. that beta-blockers are the first-line treatment for preventing the first bleeding episode, that endoscopic sclerotherapy is not indicated, and that endoscopic band ligation as an alternative to beta-blockers in this clinical setting should be further investigated) were not challenged. The attention of the experts focused on the following points:

Monitoring beta-blockade. Increasing the dose of beta-blockers to achieve a 25% reduction in resting heart rate or down to 55 b.p.m. or development of symptoms are the most commonly used approaches for adjusting the dose of beta-blockers in cirrhotic patients. Some, but not all, patients treated with beta-blockers achieving these targets will be protected from variceal bleeding. However, there is no relationship between reduction in portal pressure or protection from variceal bleeding and the degree of beta-blockade, as assessed by the reduction in resting heart rate.

A reduction in HVPG below 12 mmHg – or more than 20% from baseline – is the only tested parameter to detect those patients treated with beta-blockers who are protected from variceal bleeding. However, since about 60% of patients treated with beta-blockers who do not achieve these targets will not bleed (for 2 years) (10), in primary prophylaxis it is not mandatory to check the HVPG response.

Treatment of patients with contra-indications or intolerance to beta-blockers, or non-compliant. There is no consensus about how we should treat patients with large esophageal varices (more than 5 mm in size) who have contraindications or intolerance to beta-blockers. There are no published studies specifically addressing this issue. However, preliminary data suggest that isosorbide-5-mononitrate may not be a good alternative. Preliminary data with prophylactic endoscopic band ligation are encouraging in high-risk patients, but more studies are needed in patients with contraindications.

There is no consensus on how to treat non-compliant patients.

Combination of treatments. Available evidence is insufficient to support the use of combination therapy with beta-blockers and nitro-vasodilators in the prevention of the first variceal bleed. The combination of endoscopic treatment and pharmacologic therapy cannot be recommended at present because there are no data to support its use.

Indications for treatment and follow-up. Based on available data, there is no indication to treat patients with *small* varices. All patients with *large* varices should be treated. Additional endoscopic signs do not influence the indication for therapy. There is no need for follow-up endoscopy in patients on pharmacologic therapy.

Future studies. Trials of prophylactic band ligation in high-risk patients with contraindications or intolerance to beta-blockers are encouraged. In the absence of specific data, randomized controlled trials should be performed in patients with gastric varices.

Treatment of acute bleeding from esophageal varices

Timing of endoscopy. Endoscopy should be performed as soon as possible after admission (within 12 h), especially in patients with clinically significant bleeding or in patients with features suggesting cirrhosis. In mild bleeds, neither causing hemodynamic changes nor requiring blood volume restitution, endoscopy can be done electively.

Blood volume restitution. Blood volume restitution should be done cautiously and conservatively, using packed red cells to maintain the hematocrit between 25–30%, and plasma expanders to maintain hemodynamic stability.

Further data are required on the need for treating coagulopathy and thrombocytopenia.

Use of antibiotics for preventing bacterial infections/spontaneous bacterial peritonitis. The presence of infection should be considered in all patients. Antibiotic prophylaxis is an integral part of therapy and should be instituted from admission. Randomized controlled trials of oral non-absorbable *vs*. systemic antibiotics are needed.

Prevention of hepatic encephalopathy. Lactulose

should be given by mouth, naso-gastric tube, or enema to prevent hepatic encephalopathy.

Assessment of prognosis. The Child-Pugh classification is not sufficient to assess individual risk and prognosis, and the additional utility of other prognostic indicators should be assessed. The effect of other chronic diseases, renal failure, bacterial infections, HCC and active bleeding at endoscopy should be evaluated. Portal pressure monitoring should be further investigated.

Use of balloon tamponade. Balloon tamponade should only be used in massive bleeding as a temporary "bridge" until definitive treatment can be instituted.

Pharmacologic treatment. In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before diagnostic endoscopy. Even if there is no active bleeding at endoscopy, it is recommended to perform endoscopic therapy, especially in high-risk patients. Drug therapy may be maintained for up to 5 days to prevent early rebleeding. Randomized controlled trials should be done to determine the optimal duration.

Endoscopic treatment. In acute bleeding either ligation or endoscopic sclerotherapy can be used. For subsequent treatment, endoscopic banding ligation is replacing injection sclerotherapy as first-line endoscopic treatment for bleeding esophageal varices. Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy.

Treatment of bleeding from portal hypertensive gastropathy (PHG)

The incidence of acute PHG bleeding is low (less than 3% at 3 years); for chronic bleeding, it is around 10–15% at 3 years (9).

Treatment of acute bleeding. Vasoactive drugs are anecdotally used with a high success rate (70–100%) in uncontrolled studies. Emergency transjugular intrahepatic porto-systemic shunt (TIPS) or shunt surgery should be regarded as rescue treatments in failures of vasoactive drugs for PHG lesions likely to respond to a portal pressure decrease (excluding GAVE). The utility of Argon plasma coagulators should be evaluated.

Treatment of chronic bleeding. β-blockers, and if needed iron, are the first-choice treatment. Combined β-blockers and isosorbide-5-mononitrate, as well as other medical treatments (i.e. long-acting somatostatin analogues), should be evaluated. Treatment should be continued indefinitely.

Treatment of bleeding gastric varices

The following hypotheses need to be tested by appropriate randomized controlled trials:

- Acrylate glue injection is effective for acute gastric varices (GV) bleed.
- Endoscopic variceal sclerotherapy (EVS) (EtOH, ethanolamine oleate) is an alternative.
- Vasoactive drugs could be used in combination with other treatments.
- Banding needs evaluation.
- TIPS and surgery are indicated as rescue therapy.

Prevention of rebleeding from esophageal varices

First-line treatments. Either beta-blockade or band ligation is the first-line treatment method for prevention of recurrent variceal hemorrhage. Patients with advanced liver disease should be evaluated for liver transplantation. Combinations of endoscopic and drug treatments should be further investigated.

Treatment of patients with contra-indications to beta-blockers. Band ligation is the preferred treatment to prevent recurrent variceal hemorrhage in patients who have a contraindication to beta-blocker therapy or who have bled while on beta-blockers.

Treatment for patients who fail first-line therapy. Surgical shunt or TIPS is the recommended treatment for *good*-risk patients who fail first-line treatments (beta-blockers/banding) for prevention of recurrent bleeding. TIPS is the recommended treatment for selected *high*-risk patients who fail the preferred first-line treatments (beta-blockers/banding) for prevention of recurrent bleeding. These patients should be considered for liver transplantation.

Future studies. Future trials for secondary prophylaxis should include two or more of the following treatment arms: a) Beta-blockers±Nitrates; b) Band ligation±drug therapy; c) TIPS; d) Distal spleno-renal shunt; e) Small diameter shunts; f) Other portal hypotensive drugs ±Beta-blockers g) Combination of treatments.

Cost and quality of life evaluations should be done in future trials.

Prevention of rebleeding from gastric varices

The following treatment options need to be tested by appropriate randomized controlled trials: long-term glue injection, TIPS, surgical shunt (for good-risk patients), drug therapy.

Complications of Treatments for Portal Hypertension

Complications of pharmacological treatments

The following definitions were agreed upon:

Fatigue. Inability to perform regular physical activities carried out before treatment.

Abdominal cramps. Abdominal pain starting after

treatment that persists for more than 4 h after other major causes of abdominal pain (i.e. bacterial peritonitis) have been ruled out.

Severe bradycardia. Reduction of heart rate to a value below 50 b.p.m. during treatment, in the presence of symptoms.

Arterial hypertension. Systolic blood pressure >170 mmHg and/or diastolic blood pressure >95 mmHg during treatment in a non-hypertensive patient.

Arterial hypotension. Reduction in mean arterial pressure of 25% or greater with respect to baseline values with a final value of <70 mmHg.

Headache. Appearance of headache or worsening of pre-existing headache not responsive to usual analgesic drugs.

Complications of endoscopic treatments

Esophageal ulcers. Large, confluent esophageal ulcers 2 weeks or more after the last session of endoscopic treatment, in the presence of symptoms.

Bleeding from esophageal ulcers. Upper GI bleeding with one of the following: a) active bleeding at the ulcer site; b) adherent clot at the ulcer site; or c) absence of other potentially bleeding lesions at upper GI endoscopy.

Dysphagia. Dysphagia 1 week or more after treatment.

Esophageal stricture. Persistent narrowing of the esophageal lumen, as diagnosed by esophagogram or endoscopy, associated with dysphagia 2 weeks or more after treatment.

Chest pain. Non-cardiac chest pain requiring analgesics after treatment, persisting for more than 48 h.

Complications of TIPS

TIPS dysfunction. There was agreement on the use of angiography and/or pressure measurements when there are clinical signs of TIPS dysfunction, such as reappearance of esophageal varices or ascites.

There was no agreement on whether or not TIPS dysfunction should be assessed in patients not developing esophageal varices or ascites and which technique should be used.

Hepatic encephalopathy post-TIPS. In patients without hepatic encephalopathy before TIPS: development of clinical episodes of encephalopathy. In patients with hepatic encephalopathy before TIPS: increase in the frequency and/or intensity of episodes of encephalopathy.

Methodological Requirements for Future Trials in Portal Hypertension

Randomized controlled trials in portal hypertension should: a) include a sufficient number of patients, based on appropriate sample size calculation; b) preferably be multicenter; c) preferably use stratified randomization/minimization; d) preferably report quality of life; e) preferably report health economics.

Prognostic stratification (progstrat)

Consensus statements of previous meetings:

- Groningen, 1986. Progstrat at randomization needed at least for description of patients.
- Baveno, 1990. Progstrat in randomization and analysis.
- Baveno, 1995. RCTs results in major prognostic subgroups should be reported.
- Reston, 1996. RCTs results in major prognostic subgroups should be reported. Therapeutic benefit and harm should be interpreted according to baseline risk.

Baveno III consensus statements. Knowledge of different treatment effect according to the patient characteristics may be clinically important. Stratification of patients according to a few important prognostic variables allows proper evaluation of different subgroup treatment effects in meta-analyses if single RCTs do not reach adequate power. Stratified analysis is justified a) if a prior hypothesis is made in planning the study; b) to validate hypotheses from previous studies; c) if it is made explicit that it is a *post-hoc* analysis.

Post-hoc subgroup analyses may be considered only explorative of plausible hypotheses. Subgroup effects should be replicated in other studies and/or confirmed by meta-analysis before being accepted for clinical practice.

Quality of life evaluation

In patients with portal hypertension, both the disease and its treatment are likely to have a significant impact on quality of life. Future studies on portal hypertension should, thus, measure Health-Related Quality of Life as one of the (major) outcomes.

At present, there is no disease-specific instrument for patients with portal hypertension that has all the essential properties for measurement of HRQOL (validity, reliability, responsiveness/sensitivity, and coverage). While instruments to measure HRQOL are being developed and validated for patients with portal hypertension, generic and chronic liver disease specific instruments may be used in trials.

Health economics evaluation

Higher survival and effectiveness are the primary reasons for choosing a treatment for portal hypertension. Future RCTs on portal hypertension should be planned to record at least the event-based basic details

about the cost of therapy. The adequacy of the time horizon, sample size and the protocol-driven costs should be clearly stated.

The methodology for health economic assessment in portal hypertension should be a topic on a future consensus conference.

Conclusions

The purpose of the consensus definitions about the variceal bleeding episode and complications of treatments is to use them in trials and other studies on portal hypertension. This does not mean that authors cannot use their own definitions, but they are encouraged to use and evaluate in parallel these Baveno III consensus definitions. This should result in some measure of standardization and increased ease of interpretation among different studies. Equally important, if there are uniformly defined end-points, meta-analyses will be based on more homogeneous studies, which is an essential pre-requisite of this methodology. It is desirable that future studies be reported using these definitions as part of the evaluation. Change or refinement can then take place, as they have at Baveno III with respect to Baveno II and Reston, to ensure that the consensus definitions do have clinical relevance and are easily applied in practice. Several definitions agreed upon in Baveno I (2) and II (3,4) were taken for granted and not discussed in Baveno III. Interested readers can refer to the Baveno I and II reports (2–4).

As far as the statements concerning diagnostic algorithms, natural history and treatment strategies are concerned, they are based on the evidence emerging from the recent literature; where such evidence is weak or nonexistent, the statements reflect the prevailing current opinion among the experts.

The suggestions about the topic of future studies also reflect the opinions of the experts about the areas where new information is most needed.

As long as new diagnostic tools and new treatments appear, they will have to be assessed in comparison with present-day standards.

Acknowledgement

The Baveno III workshop was endorsed and supported in part by an unrestricted educational grant of the European Association for the Study of the Liver (EASL).

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Participants

The following chaired sessions or gave review lectures during the Workshop:

Jaime Bosch, M.D., Barcelona, Spain; Andrew K. Burroughs, M.D., London, U.K.; Gennaro D'Amico, M.D., Palermo, Italy; Juan Carlos Garcia-Pagàn, M.D., Barcelona, Spain; Guadalupe Garcia-Tsao, M.D., New Haven, CT, U.S.A.; Pere Ginès, M.D., Barcelona, Spain; Christian Gluud, M.D., Copenhagen, Denmark; Norman D. Grace, M.D., Boston, Mass. U.S.A.; Roberto Groszmann, M.D., New Haven CT, U.S.A.; Loren Laine, M.D., Los Angeles, Ca, U.S.A.; Didier Lebrec, M.D., Clichy, France; Carlo Merkel, M.D., Padua, Italy; Massimo Primignani, M.D., Milan, Italy; Massimo Pinzani, M.D., Florence, Italy; Juan Rodès, M.D., Barcelona, Spain; Shiv K. Sarin, New Delhi, India; Detlef Schuppan, M.D., Erlangen, Germany; Thorkild I.A. Sørensen, M.D., Copenhagen, Denmark; Gregory van Stiegmann, Denver, Col., U.S.A.

The following participated in the presentations and the discussion as panellists:

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