UPDATE ON THE MANAGEMENT OF PORTAL HYPERTENSION IN HCV CIRRHOSIS

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Thabut J Hepatol 2012
New Molecular Aspects in Sinusoids in Portal Hypertension

Bosch  J Hepatol 2015
From Baveno I to Baveno VI
International Workshop on Portal hypertension

- 1990: Baveno I
- 1995: Baveno II
- 2000: Baveno III
- 2005: Baveno IV
- 2010: Baveno V
- 2015: Baveno VI*

*Baveno, lake Maggiore, Italy

Definition of Clinically Significant Portal Hypertension (CSPH)

- Portal hypertension is defined by an hepatic vein pressure gradient (HVGP) > 5 mmHg.

- CSPH is defined by an increase of HVPG to a threshold ≥ 10 mmHg.

- The presence of varices, variceal hemorrhage and or ascites are complications of portal hypertension.
Screening for CSPH

- All cirrhotic patients should be screened for the presence of varices at the time of initial diagnosis of cirrhosis.

- In compensated patients with no varices at screening endoscopy and with ongoing liver injury (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 (lack of SVR in HCV), surveillance endoscopy should be repeated at one year intervals (5;D).
Screening for CSPH

- In compensated patients with no varices at screening endoscopy in whom the aetiological factor has been removed (e.g. achievement of SVR in HCV) 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) and who have no co-factors (e.g. obesity), surveillance endoscopy should be repeated at two year intervals (5;D).
Incidence and Progression of varices

■ Incidence of varices
  ■ 10-15% / year

■ Progression to small varices
  ■ 5% / year

■ Progression from small to large varices
  ■ 10-15% / year

■ HVGP is the strongest predictor of the development of varices
Hepatic Vein Pressure Gradient

- HVPG correlates significantly with fibrosis (Sheuer score)

- HVPG $\geq 10$ mmHg is the strongest predictor to develop varices
  - Grossman RJ et al, NEJM 2005; 353: 2254-

- HVPG $\geq 10$ mmHg is an independent predictor of decompensation in patients with compensated cirrhosis

- HVPG is an independent predictor of outcome (6/9 studies)

- A decrease of HVPG $\geq 20$ % of baseline or HVPG $\leq 12$ mmHg after chronic treatment with NSBB are clinically relevant for acute response to NSBB.
Definition of Key Events

Failure to control bleeding (needs to change treatment) if

- Time frame for the acute episode of bleeding should be 5 days.
- One criterion defines failure
  - Fresh hematemesis > 2h after start of specific drug treatment or therapeutic endoscopy. In patients who have a nasogastric, aspiration greater then 100 ml of fresh blood
  - Development of hypovolemic shock
  - 3 gram drop in Hb (= 9% Ht) in those non transfused. The time frame needs to be validated
  - Death.
Definition of Key Events

Failure of secondary prophylaxis

- Failure to prevent rebleeding is defined as a single episode of clinically significant rebleeding from portal hypertensive sources after day 5 (5;D).

- Clinically significant rebleeding:
  - Recurrent melena or hematemesis resulting in any of the following:
    - hospital admission
    - blood transfusion
    - 3 g drop in Hb
    - death within 6 weeks
Pre-primary prophylaxis
**Pre Primary Prevention: No advantages for β-blokers**

Double Blind Randomised Study (timolol vs placebo)  
Intend to Treat Results  
Patients with Portal Hypertension with varices

<table>
<thead>
<tr>
<th></th>
<th>Timolol (n = 108)</th>
<th>Placebo (n = 105)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparition of varices</td>
<td>42</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Death or LT</td>
<td>17</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>20</td>
<td>6</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Pre-primary Prophylaxis
Prevention of Appearing of Varices

- Pre-primary prophylaxis should only include patients without gastro-oesophageal varices. (5;D)

- 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).

- HVPG > 10 mmHg is predictive of varices formation and decompensation (1;A)

- There is no indication, at this time, to use beta-blockers to prevent the formation of varices. (1b;A)
PRIMARY PROPHYLAXIS
Prevention of the first bleeding episode
Prevention of Varices Progression
Primary Prophylaxis:

Control Randomised (nadolol vs placebo)
Résults intent to Treat
Patients with small size eesophagal varices

<table>
<thead>
<tr>
<th></th>
<th>Nadolol (n = 83)</th>
<th>Placebo (n = 78)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravation of varices</td>
<td>9</td>
<td>29</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Death or LT</td>
<td>28</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Side effects</td>
<td>9</td>
<td>1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Merkel C et al, Gastroenterology 2004; 127 (2): 476-84
Prevention of the first bleeding episode

Patients with small varices

- Patients with small varices with red wale marks or Child C class have an increased risk of bleeding (1b;A) and should be treated with nonselective beta blockers (NSBB) (5;D)

- Patients with small varices without signs of increased risk may be treated with NSBB to prevent progression of varices and bleeding. (1b;A)

- Further studies are required to confirm their benefit.
Primary Prophylaxis

Banding vs β-blokers

Méta-analysis : 7 randomised Studies

- **Haemorragic Risk**:  
  - β-blokers : 65/278 : 23%  
  - Banding : 38/276 : 14%

- In favor of Banding \( RR : 0.64 \) (0.40-1.01)

  En incluant toutes les études + Abstracts):  
  - In favor of banding \( RR : 0.63 \) (0.46-0.87)

- **No difference in survival** \( RR : 0.98 \)

- No benefit for combination β-blokers + banding vs banding (1 randomised study)
Primary Prophylaxis: Banding vs betablokers

Meta-analysis: 9 studies with 734 patients

Banding reduce oesophageal bleeding with less side effects but do not improve survival.

No significant difference in survival

Primary prophylaxis:
Primary prophylaxis: Medium-large varices (1)

- Either NSBB or endoscopic band ligation (EBL) is recommended for the prevention of first variceal bleeding of medium or large varices. (1a; A)
- Choice of treatment should be based on local resources and expertise, patient preference, characteristics, side effects and contraindications. (5; D)
- 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.
- Shunt therapy, endoscopic sclerotherapy and IMN should not be used in the first variceal bleeding prophylaxis.
Primary Prophylaxis: Gastric varices

- 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).
Primary Prophylaxis: Role of HVGP

- 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 ≤12 mmHg after chronic treatment with NSBB is clinically relevant in the setting of primary prophylaxis (1b;A).
- Similarly, acute HVPG response to IV propranolol may be used to identify responders to beta blockers, specifically a decrease in HVPG of 10% or to ≤12 mmHg may be relevant in this setting (1b;A).
Primary Prophylaxis (Role of HVGP)

- 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).
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).
Treatment of the Bleeding Episode
Treating of the Acute Bleeding Episode

Blood volume restitution

- 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,
- Transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status and ongoing bleeding (1b; A).
## Erythromycin Infusion prior to Endoscopy in Patients with Upper GI bleeding

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>N° of Patients/ patients with cirrhosis</th>
<th>Empty stomach</th>
<th>Need for second look endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frossard JL et al</td>
<td>Erythromycin (E)</td>
<td>51/13</td>
<td>82% *</td>
<td>12% *</td>
</tr>
<tr>
<td></td>
<td>Placebo (P)</td>
<td>54/19</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>Coffin B et al</td>
<td>E + Gastric lavage</td>
<td>19/4</td>
<td>90% *</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Gastric lavage</td>
<td>22/9</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Carbonnel N et al</td>
<td>E + Gastric lavage</td>
<td>49/32</td>
<td>70% *</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>P + Gastric lavage</td>
<td>50/33</td>
<td>48%</td>
<td>24%</td>
</tr>
</tbody>
</table>


* p < 0.05
Antibioprophylaxis Reduce Mortality

Metaanalysis: 8 Randomized trials: 864 patients

- Reduction of incidence of bacterial infections: RR 0.40 (95%CI: 0.32-0.51)

*Trials showed no significant heterogeneity

Soares-Weiser, Cochrane database Syst Rev 2002
Antibioprophylaxis: Which Antibiotics?

- **Blaise 1994**: IV/oral ofloxacin + amoxicillin/clavulinic acid versus no antibiotic
- **Gulberg 1999**: ceftriaxone (low dose, 1g) versus IV ceftriaxone (high dose, 2g)
- **Hsieh 1998**: oral ciprofloxacin versus placebo
- **Pauwels 1996**: IV/oral ciprofloxacin + amoxicillin/clavulinic acid versus no antibiotic
- **Rimola 1985**: non-absorbable antibiotics (oral gentamicin, vancomycin, and nystatin; or oral neomycin, colistin, and nystatin) versus no antibiotic
- **Rolando 1993**: imipenem + cilastin versus dextrose-saline solution
- **Sabat 1998**: ceftriaxone + oral norfloxacin versus oral norfloxacin
- **Selby 1994**: cefotaxime versus no antibiotic prophylaxis;
- **Soriano 1992**: oral norfloxacin versus no antibiotic
- **Spanish Group 1998**: oral norfloxacin versus oral ofloxacin
- **Zacharof 1997**: oral ciprofloxacin versus no antibiotic

*Treatment durations varied from one single dose up to ten days.*

Soares-Weiser, Cochrane database Syst Rev 2002
Antibioprophylaxis

- Antibiotic prophylaxis is part of therapy for patients with cirrhosis with upper GI bleeding and should be instituted from admission (1a;A).
- The risk of bacterial infection and mortality are low in patients with Child-Pugh A cirrhosis (2b;B), 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).
- IV 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 if previous quinolone prophylaxis (5;D).
Treatment of the Acute Bleeding Episode

Preventing hepatic encephalopathy

- 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).
Treatment of the Acute Bleeding Episode

Assessment of prognosis

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

Use of balloon tamponade:

- 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 24h) with intensive care monitoring and considering intubation, until definitive treatment can be instituted (5;D).
Treatment of the Acute Bleeding Episode

Pharmacological treatment

- 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).
Timing of Endoscopy

- Endoscopy should be considered as soon as possible after initial restitution (within 12 h of admission) especially in patients with clinically significant bleeding.

- In mild bleeds causing neither haemodynamic changes nor requiring volume restitution, endoscopy can be done electively (24h).
Treatment of the Acute Bleeding Episode

Endoscopy treatment:

- Following hemodynamic resuscitation, patients with upper GI bleeding and cirrhosis should undergo gastroscopy within 12 h (5;D).
- In absence of contraindications (QT prolongation), pre-endoscopy infusion of erythromycin (250 mg IV 30-120 min) 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 enables performance of endoscopy on a 24/7 basis 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).
Treatment of the Acute Bleeding Episode

Endoscopy treatment:

- **Ligation** is the recommended form of endoscopic therapy for acute oesophageal variceal bleeding (1b;A).

- Endoscopic therapy with tissue adhesive (e.g. N-butyl- cyanoacrylate) is recommended for GI bleeding from isolated gastric varices (IGV) (1b;A) and oesophageal varices type 2 (GOV2) that extend to 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 are needed.

- EVL or tissue adhesive can be used in bleeding from gastro-oesophageal varices type 1 (GOV1) (5;D).
Early TIPS Placement in acute bleeding

Early TIPS

- 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.
Early PTFE-TIPS versus Conventional Therapy in Patients at High risk of Failure
A multicenter European study

63 cirrhotic patients with Acute Variceal Bleeding
(Child-Pugh B+active bleeding or Child-Pugh C

Vasoactive drugs+Endoscopic treatment+Antibiotics

Randomization
24h of Admission

Standard therapy for 5 days
Then Secondary prophylaxis
EBL+BL

n= 31 patients

Early PTFE-TIPS (10mm)

n= 32 patients
within 24 hrs : 19 pts
48 hrs : 10 pts
72 hrs : 3 pts

If failure PTFE-TIPS as Rescue treatment

Early PTFE-TIPS versus Conventional Therapy in Patients at High risk of Failure

A multicenter European study

<table>
<thead>
<tr>
<th></th>
<th>Early PTFE-TIPS n= 32</th>
<th>Standard Therapy n=31</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free From failure to control active variceal bleeding or preventing rebleeding (12 months)</td>
<td>97%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Survival at 6 weeks</td>
<td>96%</td>
<td>67%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival at 12 months</td>
<td>86%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Management of treatment failures

- Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by TIPS with PTFE-covered stents. (2b;B)

- Rebleeding during the first 5 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)
SECONDARY PROPHYLAXIS
Prevention of bleeding recurrence
Time to start secondary prophylaxis

- Secondary prophylaxis should start as soon as possible from day 6 of the index variceal episode (5, D)

- The start time of secondary prophylaxis should be documented
Prevention of Rebleeding

- 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).
- NSBB should be used as monotherapy in patients 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 (5;D).
Prevention of Rebleeding

In patients who have bled from portal hypertensive gastropathy (PHG)

- 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).
The Debate

Deleterious Role of B Blokers in Child C Cirrhosis with Ascites?
Poor Prognosis of Patients with Refractory Ascites

Deleterious Effects of β-Blockers on Survival in Patients with Cirrhosis and Refractory Ascites

# Independent Predictors of Death in 174 Patients with Refractory Ascites

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>(95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh Score</td>
<td>1.43</td>
<td>(1.28 to 1.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Refractory ascites category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic-resistant</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic intractable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium &lt; 125 mmol/L</td>
<td>2.11</td>
<td>(1.34 to 3.34)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine &gt; 1.5 mg/dL</td>
<td>1.46</td>
<td>(0.92 to 2.29)</td>
<td>0.1</td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>2.04</td>
<td>(1.31 to 3.18)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Frequency of large-volume paracentesis</td>
<td>1.42</td>
<td>(1.25 to 1.61)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Scenario for Deleterious Effects of NSBB in Refractory Ascites

Large-volume paracentesis

Arterial hypotension

NSBB

No NSBB

No tachycardia, Renin hyper-activation

Tachycardia, No renin hyper-activation

Aggravation?

No aggravation
NSBB & the Risk of Death in Patients with Cirrhosis, without or with SBP

NSBB protects
HR=0.75 (0.581-0.968); P=0.027

NSBB aggravates
HR=1.58 (1.098-2.274); P=0.014

Hepatology Snapshot:
**Esophageal varices: Stage-dependent treatment algorithm**

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**Chronic liver disease**
- Assessment of stage (clinical and laboratory examination, ultrasound, liver stiffness)
- Findings inducing endoscopy

**Upper GI endoscopy**
- No varices
  - Small varices* no RCS
  - Small varices
    - No follow-up endoscopy
    - NSBB
    - NSBB or EBL
      - NSBB: no follow-up endoscopy
      - EBL follow-up endoscopies at 1, 6 and every 12 months

**TIPS** Rebleeding prophylaxis
- If significant rebleeding or if NSBB are not applicable and no contraindications

**Acute bleeding**
- Bleeding despite NSBB or EBL
  - Endoscopy within 12 h
    - High risk patient
    - Low risk patient
      - EBL (glue in GV)
      - Rebleeding prophylaxis: repeat ligation + continue NSBB

**Resuscitation**
- (volume replacement, Hb: 7-8 g/dl), vasoactive drugs, antibiotics

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*< 5 mm diameter
**If TIPS not possible, try bridging with endoscopic use of balloon tamponade and always consult TX
THANKS

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O Ciaccio, G Pittau et toute l’équipe
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