"Portal hypertension – Update 2018"

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Disclosures
Consultant/Advisory Board
Conatus, Exalenz, Actelion, BioVie, Brudy, BLB

Outline
- Relevance - Stages of cirrhosis
- Rationale basis of therapy
- Treatment of compensated patients
  - Preventing first decompensation
  - Preventing first bleeding and other complications
- Treatment in decompensated patients
  - Preventing further decompensation and death
- Treatment of acute variceal bleeding

Cirrhosis burden in Europe
- 29 million subjects with liver diseases in EU (alcohol, HCV, HBV, metabolic syndrome)
- Cirrhosis: 170,000 deaths per year
- HCC: 47,000 deaths per year
- 5,500 liver transplants/year
- Higher than breast cancer

The Portal Hypertension Fever
The complications of portal hypertension can be prevented or reversed by preventing the increase or by decreasing the HVPG

The Portal Hypertension Fever
Treatments aimed at correcting portal hypertension have a greater potential of changing the natural history and improving survival than local treatments

Clinical presentation of portal hypertension

Clinically-significant portal hypertension is responsible for complications of cirrhosis that define decompensation

Decrease in HVPG at SVR-24 in 226 patients with compensated cirrhosis treated with DAA

Clinically significant portal hypertension may persist despite elimination of the cause of cirrhosis

There is no etiological therapy for NASH
Effects of an intensive lifestyle intervention program on HVPG in patients with cirrhosis and obesity

**The Sport-Diet study**

Effects mediated by inhibition of pro-inflammatory cytokines and of bacterial translocation

Berzigotti et al. Hepatology 2017

Pathophysiology of Portal Hypertension

*Role of hemodynamic factors*

**A Pressure = Resistance x Blood Flow**

**Initial factor**

- **Increased Resistance**
  - (dynamic / structural)

**Late factor**

- **Increased Blood Flow**
  - (splanchnic vasodilation)

**Current treatments**

- **Increased Portal Pressure**
  - \[ \text{HVPG} > 10 \text{mmHg} \]

- **Formation of Collaterals & Varices**

- **Ascites**
- **Bleeding**
- **PSE**

**Acute HVPG response to iv Propranolol***

- **Acute responders**
  - HVPG ≥ 10% of baseline

**Carvedilol, a new NSBB with anti-α1 adrenergic activity has a greater effect decreasing HVPG**

Sinagra et al. AP & T 2014

Primary and Secondary Prophylaxis of Variceal Bleeding

**Current Guidelines**

**Prevention of First Variceal Bleeding**

- **NSBB (non-selective beta-blocker)**
  - *or*
  - **Endoscopic band ligation (EBL)**

**Prevention of Recurrent Variceal Bleeding**

- **NSBB (non-selective beta-blocker)**
  - plus
  - **Endoscopic band ligation (EBL)**

*“There is no indication for treating patients without high-risk varices”*

*Only recommended therapy for high-risk small varices*

De Franchis et al. Baveno VI, J Hepatol 2015

**First reports on the use of NSBB to prevent variceal bleeding in cirrhosis**

**THE LANCET**

*Stil valid in 2018!*

Propranolol for Prevention of Recurrent Gastrointestinal Bleeding in Patients with Cirrhosis — A Controlled Study

**New attempt at early therapy: The PREDESCI Study**

**PREventing the DEcompensation of Cirrhosis with non-selective beta-blockers**

- Cooperative, multicenter, placebo-controlled, randomized clinical trial
- Population studied: compensated cirrhotics with HVPG ≥ 10 mmHg (CSPH), without varices requiring treatment or previous decompensation (n=210)

**Acute HVPG response to iv Propranolol***

- **Acute responders** → Propranolol vs placebo
- **Non-responders** → Carvedilol vs placebo

* 0.15 mg/Kg IV; Acute Responders: ↓ HVPG ≥ 10% of baseline

Villanueva C…Bosch J. Lancet (in press)
Propranolol/Carvedilol (according to HVPG response) prevents decompensation of cirrhosis: The PREDESCI Study

First clinical decompensation

Prevention of First Variceal Bleeding

- NSBB (non-selective beta-blocker)*
- or
- Endoscopic band ligation (EBL)

Prevention of Recurrent Variceal Bleeding

- NSBB (non-selective beta-blocker) plus
- Endoscopic band ligation (EBL)

- There is no indication for treating patients without high-risk varices

*Only recommended therapy for high-risk small varices

Efficacy of propranolol mainly depends on the decrease in portal pressure (HVPG)

HVPG responders to NSBB for preventing variceal rebleeding also have a lower incidence of ascites and improved survival

Efficacy of propranolol mainly depends on the decrease in portal pressure (HVPG)

Variceal bleeding

Ascites

Survival

Modified from Bosch and Garcia-Pagan, Lancet 2003 361:952

Endoscopic band ligation of esophageal varices

- Repeat sessions of band ligation (mean 3 sessions, every 2-4 weeks), 4-8 bands per session
- Relatively safe → severe complications: 8% bleeding, 20% ulcers, 20% dysphagia (transient)
- Variceal recurrence: 60-90% at 1-year → Need of long-term endoscopic surveillance

Beta-blockers are of key importance in the prevention of variceal rebleeding: Individual patient meta-analysis

Take home message:
Don’t use EVL alone in Child B and C patients!
Statins: protecting the heart only?

Simvastatin associated with NSBB + EVL improves prognosis after variceal bleeding (BLEPS Study)

Outcomes

**Survival**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR: 0.387 (0.152 to 0.986)</td>
<td>p=0.583</td>
</tr>
</tbody>
</table>

Rebleeding

- Simvastatin associated with NSBB + EVL improves prognosis after variceal bleeding (BLEPS Study)
- Outcomes
  - Simvastatin: HR: 0.387 (0.152 to 0.986)
  - Placebo: HR: 0.583

Statins are associated with a decreased risk of decompensation and death in compensated HCV cirrhosis

**Decompensation**

- Statin user: HR 0.55 (0.39 - 0.77)
- Non-user: HR 1.00

**Death**

- Statin user: HR 0.38 (0.15 - 0.98)
- Non-user: HR 1.00

Current management of acute variceal bleeding

- Cautious volume resuscitation (aim at Hb 7-8 g/dl)
- Safe vasoactive drug (terlipressin, SMT, octreotide, 2-5 days)
- Antibiotic prophylaxis (5-7 days)
- Cautious volume resuscitation (aim at Hb 7-8 g/dl)

**TIPS** (Transjugular Intrahepatic Portal-systemic Shunt)

- A non-surgical calibrated shunt, very effective in decreasing portal pressure.
- Lower morbidity and mortality than surgical shunts, feasible in poor surgical candidates (Child-Pugh C)

Modified from Garcia-Tsao G. Gastroenterology 2010

TIPS as rescue therapy in acute variceal hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% of total</th>
<th>Child C</th>
<th>Control of bleeding</th>
<th>Mortality (4-6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormick-1994</td>
<td>20</td>
<td>8%</td>
<td>60%</td>
<td>100%</td>
<td>60%</td>
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<tr>
<td>Jalan-1995</td>
<td>19</td>
<td>16%</td>
<td>84%</td>
<td>100%</td>
<td>42%</td>
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<tr>
<td>Sanyal-1996</td>
<td>30</td>
<td>23%</td>
<td>73%</td>
<td>100%</td>
<td>40%</td>
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<tr>
<td>Baratess-1998</td>
<td>57</td>
<td>16%</td>
<td>41%</td>
<td>99%</td>
<td>29%</td>
</tr>
<tr>
<td>Azoulay-2001</td>
<td>58</td>
<td>16%</td>
<td>60%</td>
<td>90%</td>
<td>29%</td>
</tr>
</tbody>
</table>

"Treatment was a success but the patient died"

Success rate vs Funeral rate
Early TIPS improved outcomes in high-risk patients with variceal hemorrhage
• 63 patients, Child–Pugh C (score < 14), or Child–Pugh B with active bleeding
• TIPS within 72 hours of admission vs. current recommended therapy (vasoactive drugs plus endoscopic band ligation plus antibiotics)


Pre-emptive TIPS patients had better survival than those on standard therapy

Findings confirmed by two larger observational studies

TIPS is first-choice therapy in patients Child–Pugh C (<14 points)


Expandable esophageal stents
a new and safer way of tamponade

• Coated self-expanding metal stents
• Special introducer allowing placement without endoscopic control
• Safely removed endoscopically
• Highly effective in uncontrolled series

Results of a RCT confirm that ES is better and safer than tamponade
Escorsell et al. Hepatology 2016

Efficacy and safety of macitentan in patients with portopulmonary hypertension:
the randomized, placebo controlled PORTICO trial

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Study sponsor: Actelion Pharmaceuticals Ltd.
The PORTICO study

- Randomized, double-blind, placebo-controlled, prospective, multicenter study to assess the efficacy and safety of macitentan in patients with PoPH (NCT02382016)

### Diagram

- **Double-blind period**
- **Open-label period**
- **Safety follow-up 30 days**

- **Macitentan 10 mg**
- **Placebo**

- **Screening**
- **Randomization**
- **28 days**
- **Week 12**
- **Week 24**

### Primary endpoint – PVR at Week 12 expressed as ratio of baseline

- **35% reduction in PVR for macitentan vs. placebo**

- Model-adjusted* ratio of geometric means (95% CI) for macitentan:placebo
  - 0.65 (0.59, 0.72); p<0.0001

- Horizontal lines in figure are geometric mean PVR ratio Week 12:baseline for each treatment; imputed values shown in red.

*ANCOVA model on log-transformed ratio of baseline PVR with terms for treatment, region and background PAH therapy and with log PVR at baseline as a covariate.

### Acknowledgements

- www.swissliver.ch

Collaborations
- Spanish Cooperative group
- Baveno Cooperation
- Dr García-Tsao, Yale University
- Dr Juan Abraldes, Edmonton
- Dr A.Luca & G.Pietrosi, ISMETT

- G.Stirnimann
- A De Gottardi
- J-F Dufour
- S.Casu
- N Semmo